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Percutaneous Heart Valve Replacement

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Structured Abstract

Objectives: To describe the types of prosthetic heart valves now in use and in development, to summarize clinical studies completed or under way, and to discuss factors that may impact clinical outcomes for percutaneous heart valve (PHV) replacement.

Data Sources: MEDLINE®, EMBASE®, and gray literature sources.

Review Methods: We searched the English-language literature to identify systematic reviews and comparative clinical studies of conventional heart valves (CHVs) and studies of PHVs in adults. We define PHV replacement as the delivery of a prosthetic heart valve via a catheter inserted either through a femoral vein or artery (transfemoral approach) or through the apex of the heart via an incision in the chest wall (transapical approach).

Results: We identified numerous mechanical and bioprosthetic heart valves. Six systematic reviews compared various CHVs; the single high-quality review found better short-term hemodynamic performance but longer operating times with stentless compared to stented bioprosthetic valves. A large primary literature (57 randomized controlled trials, 40 observational studies) compares various CHVs.

Six PHVs were described in 32 fully published case reports or non-comparative case series that studied 542 unique patients. All but 18 of the 542 patients represented in the published literature received valves produced by one of two PHV manufacturers. A transapical approach was used in 164 patients (30 percent), with the remaining patients having undergone a

transfemoral procedure. All but one of the prosthetic valves were implanted in patients with symptomatic aortic stenosis at high operative risk. Successful implantation was achieved in 89 percent of patients; 30-day survival was 85 percent. The lack of comparative studies limits the ability to determine which variables associated with PHV replacement are causally related to outcomes. A multicenter randomized controlled trial comparing PHV to CHV replacement or medical management is currently underway in the United States.

Conclusions: A large number of heart valve prostheses are in use, but there are limited data to inform the selection of one valve over another. There is sufficient existing primary literature to support systematic reviews or meta-analyses to help inform several important clinical questions pertaining to CHV replacement. PHV replacement is a rapidly emerging technology that has been proven feasible, and it is associated with outcomes that are comparable to those of conventional heart valve replacement, although the patient populations are not directly comparable. Well-designed observational studies and decision modeling could help inform clinical and health policy in the absence of randomized clinical trials.

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Executive Summary

Introduction

As the proportion of older adults increases in the U.S. population, the prevalence of degenerative valve disease is also increasing. Calcific aortic stenosis (narrowing) and ischemic and degenerative mitral regurgitation (leakage) are the most common valvular disorders in adults aged 70 years and older. For patients with severe valve disease, heart valve replacement involving open heart surgery can improve functional status and quality of life. A variety of mechanical and bioprosthetic heart valves are readily available. However, as many as one-third of older adults with severe disease are considered too high risk for open heart surgery. These patients may benefit from a less invasive procedure.

Percutaneous heart valve replacement is an interventional procedure involving the insertion of an artificial heart valve using a catheter, rather than through open heart surgery. The first report of heart valve replacement via a percutaneous approach was published in 2002. The Agency for Healthcare Research and Quality (AHRQ) has requested a Technical Brief to summarize the available clinical and scientific evidence on percutaneous heart valves relative to traditional surgical heart valve replacement. This Technical Brief includes a description of the types of conventional and percutaneous valves now in use or in development, the types of clinical studies completed and under way, and opportunities for future research.

Methods

AHRQ originally identified four key questions to be addressed in this Technical Brief. The research team at the Duke Evidence-based Practice Center further clarified and refined the

overall research objectives and the key questions in consultation with AHRQ. The review and evidence synthesis are structured around four key goals, involving: (a) a description of valves now in use or in development; (b) a literature scan to describe studies comparing conventional valves; (c) a description of studies evaluating percutaneous valves; and (d) a description of factors associated with outcomes in percutaneous heart valve replacement.

To identify valves in use or in development, we searched MEDLINE® for English-language studies published from 1949 to December 2008; the gray literature, including pertinent scientific meeting abstracts from the past 3 years; U.S. Food and Drug Administration (FDA) records; the website, www.clinicaltrials.gov; and the websites of valve manufacturers. Based on expert recommendations, we contacted 14 companies believed to be developing percutaneous heart valves. FDA status was determined by materials from the FDA and supplementary sources.

To characterize the literature comparing conventional valves, we initially identified systematic reviews, then conducted supplementary searches to identify randomized controlled trials and observational studies. We quality-rated the reviews and abstracted data from primary data studies on basic study design, sample size, valves compared, duration of follow-up, and whether key outcomes were reported.

For percutaneous valves, we included all published reports containing primary data from adult humans. Detailed abstractions were completed for relevant study details, including patient characteristics, valve implantation approach, and hemodynamic and clinical outcomes.

Results

Heart Valves in Use and in Development

Mechanical and bioprosthetic heart valves are readily available and FDA approved for use in

the United States. Currently marketed mechanical valves utilize tilting-disc and bileaflet designs; cage-ball valves are no longer marketed. Mechanical valves are durable and are implanted using a standard procedure, but require chronic anticoagulation due to an increased risk of thromboembolic complications. Bioprosthetic heart valves utilize *stented* designs that support porcine or bovine tissue or *stentless* designs that combine the aortic root with a porcine valve. Bioprosthetic valves are less durable than mechanical valves but do not require anticoagulation. Stentless valves may offer improved hemodynamic outcomes, but their implantation is more technically demanding than the implantation of stented valves. In older adults, bioprosthetic valves are recommended and are the most commonly used type for aortic stenosis. Homograft heart valves (from human cadavers) are infrequently used because of poor availability. Tissue-engineered valves that are developed from the patient's own cells are in development but are not FDA approved.

Percutaneous heart valves are in development and approved for use in some parts of Europe; none are FDA approved for use in the United States. Percutaneous heart valves are a type of bioprosthetic valve constructed out of bovine, porcine, or equine tissue, with a collapsible frame that allows delivery by a catheter. Percutaneous valves can be implanted using either a transfemoral or transapical approach. The transfemoral approach does not require sternotomy or heart-lung bypass, and has been performed using conscious sedation or general anesthesia. The transapical approach uses a mini-sternotomy to access the heart and deliver a percutaneous valve by catheter through the left ventricle. To date, these valves have been used almost exclusively in patients with severe symptomatic aortic stenosis who are considered too high risk for conventional valve surgery.

Studies Comparing Various Types of Conventional Heart Valves

We identified six relevant systematic reviews comparing various types of conventional heart valves with one another. A high-quality review synthesized results from six randomized trials comparing aortic stented to stentless bioprosthetic valves and concluded that stentless valves showed improved hemodynamics and a greater reduction in left ventricular mass at 6 months (which was not sustained at 12 months), but longer operating times. Other systematic reviews comparing mechanical to bioprosthetic valve classes (three reviews), or comparing two specific valves (two reviews), had important methodological limitations which may bias estimates of comparative effectiveness.

Our search of the primary literature identified 57 randomized controlled trials and 40 observational studies comparing two or more conventional heart valves, most often in the aortic position. Of these, 16 trials and 26 observational studies were included in the existing systematic reviews. Most trials reported outcomes at 1 year or less. Trials with long-term follow-up were conducted in patients that differ significantly from patients commonly undergoing heart valve replacement today and examined valves that are now obsolete. Observational studies have longer-term follow-up and describe outcomes in more representative patients, but are at greater risk for bias.

Studies of Percutaneous Heart Valves

Our search strategy identified 26 fully published studies, described in 32 publications and representing a total of 542 unique patients who underwent percutaneous heart valve replacement. Our gray literature search identified 12 abstracts presented at scientific meetings in 2008, representing 923 patients, some of whom may also be represented in fully published reports. All

of the studies were either non-comparative case series or single case reports. Six different valves are represented in the published literature and meeting abstracts, but most experience to date is with the Edwards SAPIEN THV (273 patients) and the CoreValve device (251 patients). The other four valves were each represented in a single published report. Percutaneous heart valve replacement was performed using a transfemoral antegrade approach in 37 patients, a transfemoral retrograde approach in 322 patients, a transapical approach in 164 patients, and a combination of two of these three approaches in 3 patients. Only a single patient represented in the eligible reports in the published literature underwent percutaneous heart valve replacement in the pulmonic position; all other patients had symptomatic aortic stenosis and had valves replaced in the aortic position. Approximately 89 percent of patients underwent successful delivery and deployment of a percutaneous valve. The vast majority of the published studies were conducted in Europe.

Thirty-day survival across all published reports was approximately 85 percent. We identified a single ongoing randomized controlled trial, the PARTNER (Placement of AoRTic TraNscathetER) trial, which compares the Edwards SAPIEN THV to conventional surgical valve repair in high-risk patients with aortic stenosis, and the Edwards SAPIEN THV to medical management in inoperable patients.

Variables that May Affect Outcomes for Percutaneous Valves

In consultation with experts in cardiology and cardiac surgery, we considered six general categories of variables that may impact outcomes for percutaneous valves: (1) prosthesis characteristics; (2) implantation approach; (3) treatment setting; (4) operator characteristics; (5) type of anesthesia; and (6) patient characteristics. The absolute lack of comparative studies

precludes determining causality of any variable as it pertains to outcomes. The data suggest, however, that the size of valve prosthesis for any of the three percutaneous approaches, and the size of the catheter used to delivery the prosthetic valve using either of the two transfemoral approaches, may be important determinants of clinical outcomes. The data support the hypothesis that operator and patient characteristics may also impact outcomes.

Discussion

A substantial literature, including trials and observational studies, compares conventional heart valves. Existing systematic reviews are limited by the methods employed and the quality of the primary literature. Some important comparisons (e.g., differing mechanical designs) have not been the subject of a review. Challenges to a high-quality systematic review include: studies incorporating obsolete and currently marketed valves; varying duration of follow-up; inconsistent reporting of valve names; and incorporating data from trials and observational studies.

Percutaneous heart valves are being developed by at least six companies. Most of the published literature originates from Europe and involves the CoreValve and Edwards Sapien valves. This literature describes the short-term experience in 542 adults, reporting implantation rates of about 90 percent and 30-day survival of about 85 percent. Abstracts from recent scientific meetings report results in an additional 900 subjects, suggesting a rapidly increasing experience. Transfemoral retrograde and transapical are the currently preferred approaches. The literature demonstrates the feasibility of percutaneous heart valve replacement, but is inadequate to determine the effectiveness of percutaneous valves compared to conventional valves, the effects on overall mortality in the high-risk patients studied to date, the technical approaches that

optimize outcomes, and the appropriate patients for this procedure. If the PARTNER trial demonstrates efficacy, percutaneous valves may expand the indications for valve replacement surgery.

Future Research

Important clinical issues in selecting a heart valve include the technical difficulty of valve replacement, valve durability, hemodynamic performance, complication rates, the need for anticoagulation, and effects on important patient outcomes such as functional status and mortality. Clinical decisionmaking and policy could be informed by:

- A high-quality systematic review that carefully evaluates important conventional valve comparisons, including newer bioprosthetic versus mechanical valves and tilting disc versus bileaflet mechanical valves.
- Observational studies that link databases that record long-term outcomes (e.g., Medicare claims data) to clinical databases in order to allow better adjustment for confounding.
- Randomized trials comparing newer valve devices, such as percutaneous valves, to conventional valves. The ongoing PARTNER trial is an example of this type of study.
- Device registries of new heart valve technologies that would allow for more rapid and less expensive evaluations compared to randomized trials.
- Decision modeling that incorporates clinical issues (such as valve durability) and patient characteristics (such as competing risk for mortality), procedure costs, and patient preference.

Conclusion

Because the U.S. population is aging and aortic and mitral valve disease is age-related, heart valve replacement is an important issue both clinically and from the perspective of healthcare policy. Conventional heart valve replacement is a well-established intervention with many available device options, but current evidence syntheses do not provide sufficient evidence to select specific valves. A high-quality systematic review that addresses important valve comparisons could help decisionmaking.

Many older adults are not currently candidates for conventional heart valve replacement. Percutaneous valve replacement has been demonstrated to be feasible, and short-term outcomes are promising. The PARTNER trial will provide the first comparison of percutaneous to conventional valves. If effective, percutaneous valves have the potential to expand access to valve replacement for a large group of older adults with severe valve disease and concurrent medical conditions that currently preclude surgery. Percutaneous valves also have the potential to substitute for some conventional valve replacements and expand the indications for valve replacements.

Technical Brief

Chapter 1. Introduction

Background

As the proportion of older adults increases in the U.S. population, the prevalence of degenerative valve disease is also increasing. Calcific aortic stenosis (narrowing) and ischemic and degenerative mitral regurgitation (leakage) are the most common valvular disorders in adults aged 70 years and older.[1, 2] For patients with severe valve disease, heart valve replacement involving open heart surgery can improve functional status and quality of life.[3-5] A variety of mechanical and bioprosthetic heart valves are readily available. However, some individuals are considered too high risk for open heart surgery. These patients may benefit from a less invasive procedure.

Percutaneous heart valve replacement is an interventional procedure involving the insertion of an artificial heart valve using a catheter, rather than through open heart surgery.[6] The Agency for Healthcare Research and Quality (AHRQ) has commissioned a Technical Brief to summarize the available clinical and scientific evidence on percutaneous heart valves relative to traditional surgical heart valve replacement. This Technical Brief includes a description of the types of valves now available or in development, and the types of clinical studies completed and under way in adults.

Epidemiology

Aortic stenosis and mitral regurgitation are the most common valvular disorders in older adults. The prevalence of at least moderate aortic stenosis in the general population increases from 2.5 percent at age 75 to 8.1 percent at age 85.[7] Once moderate aortic stenosis (valve area

1.0 to 1.5 cm^2) is present, the valve area decreases at an average rate of 0.1 cm^2 per year. After a long latent period, patients may develop symptoms of angina, syncope, or heart failure with moderate, or more commonly, severe stenosis. The decision to replace the aortic valve is based largely on the presence or absence of symptoms.[8] After the onset of symptoms, the risk of sudden death is high, and survival averages 2 to 3 years.[9-12] Aortic valve replacement (AVR) is the most common heart valve operation, accounting for 60 to 70 percent of all valve surgery performed in the elderly. In adults with severe, symptomatic, calcific aortic stenosis, AVR is the only effective treatment.[8] In patients with symptomatic aortic stenosis, AVR improves symptoms, functional status, and survival. The 2006 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines make a Class I recommendation for AVR in symptomatic patients with severe aortic stenosis.[8] AVR is also recommended in certain circumstances for patients with severe stenosis who are asymptomatic, and for patients with mild to moderate stenosis. Aortic valve repair using balloon valvoplasty has been performed in older adults, but results in poor outcomes and is only considered for patients considered too high risk for valve replacement.

AVR carries a perioperative mortality risk of approximately 3.0 to 4.0 percent, increasing to 5.5 to 6.8 percent when combined with coronary artery bypass grafting.[4, 8] In patients over the age of 65, the average in-hospital mortality is 8.8 percent.[13] Operative risks can be estimated with validated online risk calculators[7, 14-16] that include age, sex, functional status, cardiac factors, and medical comorbidity. Although age alone is not a contraindication to surgery, a survey of Dutch cardiologists found age to be a primary determinant in the decision to recommend AVR.[17] Based on high-risk features or age, a significant subset of patients with indications for valve surgery are deemed ineligible for conventional valve replacement.[18] One

survey of 92 European heart centers found that 31.8 percent of patients with severe, symptomatic, single valve disease did not undergo intervention, most frequently because of comorbidities.[19]

Mitral valve regurgitation affects approximately 2.3 percent of 60- to 69-year-olds and 5.5 percent of adults older than 70.[1] It is the second most common reason for valve surgery in older adults. The most common causes of mitral regurgitation in older adults are myxomatous degeneration and ischemic heart disease.[20-22] With mild to moderate disease, individuals may remain asymptomatic for many years. Patients with chronic severe mitral regurgitation have a high likelihood of becoming symptomatic after 6 to 10 years. The 2006 ACC/AHA guidelines recommend mitral valve surgery for patients with chronic severe mitral regurgitation who have impaired functional status or meet specific hemodynamic criteria.[8] In contrast to the recommendations for patients with aortic stenosis, valve repair – rather than replacement – is considered an option and is recommended for "the majority of patients with severe chronic mitral regurgitation who require surgery."[8]

Valve Replacement

Conventional valve replacement requires general anesthesia, a sternotomy, and heart-lung bypass. The surgeon removes the diseased valve and replaces it with a biological or mechanical valve. Surgery averages 3 to 6 hours, and most patients are discharged from hospital after 5 to 6 days. Recovery generally takes 6 to 12 weeks. Patients who receive a mechanical valve will be placed on life-long anticoagulation that requires regular monitoring. Patients with prosthetic heart valves are at higher risk for endocarditis, and antibiotic prophylaxis is recommended for many dental, genitourinary, gastrointestinal, and respiratory tract procedures.[8]

Minimally invasive valve surgery is similar to traditional surgery but uses smaller incisions, with the potential advantages of less bleeding, less pain, and decreased recovery time. Minimally invasive surgery is technically more difficult.

Selecting the specific heart valve involves both clinical and technical considerations. Clinical considerations include: concurrent indications for anticoagulation (e.g., chronic deep venous thrombosis) or contraindications to anticoagulation; the patient's life expectancy; and patient preference. Technical considerations include: surgeon experience with particular valves; the technical difficulty of implanting differing valves; valve durability; and the size of the valve annulus.

Catheter-based implantation is an experimental approach. Two catheter-based techniques have been investigated. Initially, the valves were delivered via either the femoral artery or vein (using a "transfemoral" approach). More recently, a transapical approach has been developed. For the purpose of this report we consider both approaches to fall within the scope of percutaneous heart valve replacement. The transapical approach is performed by cardiac surgeons, using direct left ventricular apical puncture through a small thoracotomy. The procedure does not require a sternotomy. The percutaneous approach delivers the valve by catheter through the femoral vein or artery. Both techniques employ a valve that is crimped onto a catheter and deployed without removing the diseased valve. Catheter-based approaches do not require heart-lung bypass. Potential advantages include decreased recovery time and lower surgical risk. Potential disadvantages include a greater risk for valve migration (since the valve is not sewn into place), complications associated with catheter-based delivery, and uncertain valve durability.

Goals of Technical Brief

The goals of this Technical Brief are to:

- Describe the types of heart valves now in use or in development and their potential advantages and disadvantages.
- Describe the literature comparing various types of conventional heart valves in adults and determine whether a systematic review of this literature is feasible and needed.
- Describe the literature evaluating percutaneous heart valves in adults, including the patient populations and major outcomes studied to date.
- Describe implantation techniques for percutaneous valves and the factors associated with surgery or setting that may impact outcomes.

Chapter 2. Methods

This chapter provides an overview of the methods used to develop this Technical Brief. More detailed information on the methods used in relation to individual key questions is provided in Chapters 3-6.

Topic Assessment and Refinement

The Agency for Healthcare Research and Quality (AHRQ), sponsor of this report, originally identified four key questions to be addressed in this Technical Brief. The research team at the Duke Evidence-based Practice Center (EPC) further clarified and refined the overall research objectives and the key questions in consultation with the AHRQ Task Order Officer assigned to the project.

At the most general level, the objectives of this report are: (a) to describe the heart valve replacement options available to adults; and (b) to summarize the available clinical and scientific evidence on conventional and percutaneous heart valves for adults with valvular heart disease.

The key questions considered are as follows (content as agreed upon with AHRQ; the order of the questions has been changed slightly from the original to facilitate the presentation of results):

Question 1: What are the different types of heart valves in use and in development (including tissue, mechanical, and percutaneous valves)?

a. What are the existing or potential U.S. Food and Drug Administration (FDA) indications for each valve (patient characteristics, etc.)?
b. What are the theoretical advantages and disadvantages of different valves for

different patient populations?

Question 2: From a systematic literature scan of studies on different types of tissue and mechanical valves, describe the types of comparative studies, including basic study design, size of study, length of follow-up, and outcomes assessed. This literature scan will provide data to determine if a systematic review of this literature is possible and needed, and to provide needed context for understanding the evaluation and development of percutaneous heart valves.

Question 3: From a systematic literature scan of studies on different types of percutaneous heart valves, provide a synthesis of the following variables:

a. Number for each type of valve.
b. Type of studies – comparative and non-comparative randomized controlled trials (RCTs), non-randomized controlled clinical trials (CCTs), case series, etc.
c. Variables associated with surgery (implantation technique), setting, etc.
d. Size of studies/length of follow-up.
e. Patient population/concurrent and prior treatments.
f. Hemodynamic success rates reported.
g. Harms reported.

Question 4: What are the variables associated with surgery or setting that may impact outcomes for percutaneous heart valves?

a. What are the different implantation techniques (i.e., position of implantation, delivery, and axis techniques)? What is the evidence of success (i.e., absence of narrowing and regurgitation) and harms?
    i. For percutaneous aortic valves
    ii. For percutaneous mitral valves

Sources of Information and Review Methods

The sources of information consulted and review methods used by the Duke team varied considerably by key question. Question 1 involved gathering and collating information from the FDA, device manufacturers, and other sources. Question 2 and Questions 3-4 required separate literature reviews using distinct sources, search strategies, and review methods. Because of this variability, the methods used for each key question are described in a separate section near the beginning of the relevant chapter below.

Peer Review Process

We employed internal and external quality-monitoring checks through every phase of the project to reduce bias, enhance consistency, and verify accuracy. Examples of internal monitoring procedures include: three progressively stricter screening opportunities for each article (abstract screening, full-text screening, and data abstraction); involvement of at least two individuals (an abstractor and an over-reader) in each data abstraction; and agreement of at least two clinicians on all included studies.

Our principle external quality-monitoring device is the peer-review process. Nominations for peer reviewers were solicited from several sources, including the clinical content experts on the Duke research team, AHRQ, and staff at the Scientific Resource Center (SRC) at the Oregon EPC. The list of nominees was forwarded to AHRQ for vetting and approval. A list of peer reviewers submitting comments on this draft will be included in an Appendix to the final report.

Chapter 3. Heart Valves in Use and in Development (Question 1)

Methods

Question

Question 1 was: What are the different types of heart valves in use and in development (including tissue, mechanical, and percutaneous valves)?

a. What are the existing or potential U.S. Food and Drug Administration (FDA) indications for each valve (patient characteristics, etc.)?
b. What are the theoretical advantages and disadvantages of different valves for different patient populations?

Approach

We used four approaches to identify heart valves now in use or in development. First, we identified valves described in the published literature abstracted in answer to Question 2 (conventional valves) and Questions 3 and 4 (percutaneous valves). Next, we generated a list of valve manufacturers based on the published literature and expert knowledge. The Scientific Resource Center (SRC) at the Oregon Evidence-based Practice Center (EPC) then contacted 14 companies believed to manufacture percutaneous heart valves on our behalf and requested information on percutaneous valves in use or in development. (They attempted to contact a 15th manufacturer, but were unable to identify any current contact information for the company.) Of the 14 manufacturers contacted, seven did not respond, six responded that they had nothing to submit, and one – Edwards LifeSciences, LLC – responded with the requested information.

Finally, we supplemented these approaches by searching the websites of valve manufacturers.

To identify valves with FDA approval, we first contacted the FDA, who provided a list of approved valves. For valves known to us but not included in the list provided by the FDA, we searched the Internet using the search engine Google and terms for the manufacturer, the specific valve, and "FDA." Using this strategy, we discovered and accepted manufacturer press releases claiming FDA approval.

Percutaneous heart valves are an emerging technology, and none is FDA approved. For this valve class, we relied on the published literature and experts to describe potential FDA indications.

To determine the theoretical advantages and disadvantages of different valves for different populations, we relied on discussions and recommendations in clinical guidelines, review articles, and consultations with experts. Using these sources, we developed a narrative description of the valves classes, goals in valve design, and the theoretical advantages and disadvantages of different types of valves.

Results

Listing of Valves

Table 1 (conventional valves) and Table 2 (percutaneous valves) summarize the information we were able to compile, using the methods described above, on heart valves now in use or in development and their FDA status. In many instances, valve names used in the published literature were incomplete and did not precisely match device names provided by manufacturers or the FDA. In such cases, we attempted to match names based on other device characteristics, such as valve type, or from narrative descriptions in the literature. When matches could not be

made with confidence, we listed all valve device names. Thus, Tables 1 and 2 may list some valves more than once using different names. Some of the valves listed are no longer manufactured but may be encountered in patients with past valve replacements. These obsolete valves are also described in reviews and primary comparative studies. For these reasons, we included these valves in our summary tables.

Table 1. Conventional heart valves in use or in development

Company	Valve name	Valve position	Valve type*	FDA indication?†	Notes‡
Mechanical valves					
Alliance Medical Technologies	Monostrut Cardiac Valve Prosthesis	Unknown	Tilting disc	Yes (FDA)	No longer marketed (FDA)
Aortech	Ultracor	Aortic	Tilting disc	Unable to determine	
ATS Medical, Inc.	Bioflow	Unknown	Unknown	Unable to determine	
ATS Medical, Inc.	Open Pivot Bileaflet Heart Valve	Mitral & aortic	Bileaflet	Yes (FDA)	
Bjork-Shiley	Convex/Concave	Unknown	Tilting disc	Unable to determine	
Bjork-Shiley	Low Profile	Unknown	Tilting disc	Unable to determine	
Bjork-Shiley	Monostrut	Mitral & aortic	Tilting disc	Yes (non-FDA)	No longer marketed (non-FDA)
Carbomedics, Inc.	CarboMedics Prosthetic Heart Valve	Unknown	Bileaflet	Yes (FDA)	
Carbomedics, Inc.	CarboMedics Valve	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models
Carbomedics, Inc.	Carbo-Seal Ascending	Aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models
Carbomedics, Inc.	Carbo-Seal Valsalva	Aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models
Carbomedics, Inc.	Optiform	Mitral	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models
Carbomedics, Inc.	Orbis Universal	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models
Carbomedics, Inc.	Pediatric/Small Adult	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models

Company	Valve name	Valve position	Valve type*	FDA indication?†	Notes‡
Carbomedics, Inc.	Reduced Series Aortic	Aortic	Bileaflet	Yes (non-FDA)	
Carbomedics, Inc.	Standard Valve	Mitral & aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models
Carbomedics, Inc.	Top Hat Suppra-Annular	Aortic	Bileaflet	Yes (non-FDA)	FDA indicates that the Carbomedics Prosthetic Heart Valve has FDA indication, but does not specify which models
Direct Flow Medical, Inc.	Website under construction – no information	Unknown	Unknown	Unable to determine	
Edwards Lifesciences, LLC	Edwards Duromedics	Mitral & aortic	Bileaflet	Unable to determine	No longer marketed (non-FDA)
Edwards Lifesciences, LLC	Edwards MIRA Mechanical	Mitral & aortic	Bileaflet	Unable to determine	
Edwards Lifesciences, LLC	Starr-Edwards Silastic Ball Heart Valve Prosthesis	Mitral	Caged-ball	Yes (FDA)	No longer marketed (non-FDA)
Edwards Lifesciences, LLC	Tekna	Unknown	Tilting disc	Unable to determine	No longer marketed (non-FDA)
Lillehei-Kaster	Lillehie-Kaster Heart Valve	Mitral & aortic	Tilting disc	Unable to determine	No longer marketed (non-FDA)
Lillehie-Kaster	Low Profile	Unknown	Tilting disc	Unable to determine	No longer marketed (non-FDA)
MedicalCV	Omnicarbon Cardiac Valve Prosthesis	Aortic	Tilting disc	Yes (FDA)	No longer marketed (FDA)
MedicalCV	Omniscience Cardiac Valve Prosthesis	Aortic	Tilting disc	Yes (FDA)	No longer marketed (FDA)
Medtronic, Inc.	Advantage Supra Bileaflet	Aortic	Bileaflet	Unable to determine	
Medtronic, Inc.	Medtronic-Hall Prosthetic Mechanical Heart Valve	Mitral & aortic	Tilting disc	Yes (FDA)	
On-X Life Technologies, Inc.	On-X Prosthetic Heart Valve	Aortic	Bileaflet	Yes (FDA)	
Sorin Biomedica Cardio	Allcarbon	Mitral & aortic	Tilting disc	Unable to determine	
Sorin Biomedica Cardio	Bicarbon Family	Mitral & aortic	Bileaflet	Unable to determine	

Company	Valve name	Valve position	Valve type*	FDA indication?†	Notes‡
Sorin Biomedica Cardio	Carbocast	Mitral	Tilting disc	Unable to determine	
Sorin Biomedica Cardio	Monocast	Mitral & aortic	Tilting disc	Unable to determine	
Sorin Biomedica Cardio	Monodisk	Mitral & aortic	Tilting disc	Unable to determine	
Sorin Biomedica Cardio	Slimline	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	High Performance	Unknown	Unknown	Unable to determine	
St. Jude Medical	St. Jude Medical Coated Aortic Valved Graft Prosthesis	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters HP Valved Graft with Gelweave Valsalva Technology	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Mechanical Heart Valve with Silzone Coating	Mitral & aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Series Aortic Valved Graft	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Series Hemodynamic Plus Valve with FlexCuff Sewing Ring	Aortic	Bilfeaflet	Unable to determine	No longer marketed (non-FDA)
St. Jude Medical	St. Jude Medical Masters Series Mechanical Heart Valve	Mitral & aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Masters Valved Grat with Hemashield Technology	Aortic	Bileaflet	Unable to determine	
St. Jude Medical	St. Jude Medical Mechanical Heart Valve	Mitral & aortic	Bileaflet	Yes (FDA)	
St. Jude Medical	St. Jude Medical Mechanical Valve Hemodynamic Plus Series	Mitral & aortic	Bileaflet	Unable to determine	

Company	Valve name	Valve position	Valve type*	FDA indication?†	Notes‡
St. Jude Medical	St. Jude Medical Regent Valve	Aortic	Bileaflet	Yes (non-FDA)	
St. Jude Medical	St. Jude Medical Regent Valve with Silzone Coating	Aortic	Bileaflet	Unable to determine	No longer marketed (non-FDA)
Unknown	Debakey	Unknown	Unknown	Unable to determine	
Unknown	Hall-Kaster	Unknown	Unknown	Unable to determine	
Unknown	Harken	Unknown	Tilting disc	Unable to determine	No longer marketed (non-FDA)
Unknown	Smelloff-Cutter	Unknown	Unknown	Unable to determine	
Bioprosthetic valves					
ATS Medical, Inc.	ATS 3F Aortic Bioprosthesis, Model 1000	Aortic	Equine	Yes (FDA)	
Biocor	Biocor	Unknown	Porcine	Unable to determine	Stentless (non-FDA)
Bioflo	Unknown	Unknown	Bovine	Yes (non-FDA)	No longer marketed (non-FDA)
Carbomedics, Inc.	Mitroflow Aortic Pericardial Heart Valve	Aortic	Bovine	Yes (FDA)	
Cryolife	O'brien Model 300	Aortic	Porcine	Unable to determine	Stentless (non-FDA)
Cryolife	SynerGraft Pulmonary Valve and Valved-Conduit Allograft	Pulmonary	Human	(cleared, not approved)	Decellularized (non-FDA)
Edwards Lifesciences, LLC	Carpentier-Edwards Bioprosthesis	Aortic & Mitral	Porcine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Duraflex Low Pressure Bioprosthesis	Mitral	Porcine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Magna Pericardial Bioprosthesis	Mitral & aortic	Bovine	Yes (non-FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Pericardial Bioprosthesis	Aortic & Mitral	Bovine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Plus Pericardial Bioprosthesis	Mitral & aortic	Bovine	Yes (FDA)	Stented (non-FDA)

Company	Valve name	Valve position	Valve type*	FDA indication?†	Notes‡
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount RSR Pericardial Bioprosthesis	Aortic	Bovine	Yes (FDA)	
Edwards Lifesciences, LLC	Carpentier-Edwards Perimount Theon	Mitral & aortic	Bovine	Unable to determine	
Edwards Lifesciences, LLC	Carpentier-Edwards Supra-Annular Valve (SAV) Bioprosthesis	Mitral, Aortic, & Tricuspid	Porcine	Yes (FDA)	
Edwards Lifesciences, LLC	Edwards Prima™ Plus Stentless Bioprosthesis	Aortic	Porcine	Yes (FDA)	
Edwards Lifesciences, LLC	Prima Stentless Bioprothsthesis (Subcoronary), Model 2500	Aortic	Porcine	Yes (FDA)	No longer marketed (FDA)
Medtronic, Inc	Medtronic Contegra Pulmonary Valved Conduit (Models 200 and 200S)	Pulmonary	Bovine	Yes (FDA)	FDA approved for use as humanitarian use devices under HDEs (FDA)
Medtronic, Inc.	Freestyle Aortic Root Bioprosthesis	Aortic	Porcine	Yes (FDA)	Stentless (non-FDA)
Medtronic, Inc.	Intact	Aortic	Porcine	Unable to determine	
Medtronic, Inc.	Medtronic Hancock I (Standard) Porcine Bioprosthesis	Mitral	Porcine	Yes (FDA)	
Medtronic, Inc.	Medtronic Hancock II Bioprosthetic Heart Valve	Mitral & aortic	Porcine	Yes (FDA)	Stented (non-FDA)
Medtronic, Inc.	Medtronic Hancock Modified Orifice (MO) Porcine Bioprosthesis	Aortic	Porcine	Yes (FDA)	
Medtronic, Inc.	Medtronic Mosaic Porcine Bioprosthesis	Mitral & aortic	Porcine	Yes (FDA)	Stented (non-FDA)
Shelhigh	Biomitral	Mitral	Porcine	Unable to determine	
Shelhigh	Injectable Pulmonic Valve System	Apical Approach Pulmonic	Bovine	Unable to determine	
Shelhigh	NR2000 Plus Semistented	Aortic	Porcine	Unable to determine	

Company	Valve name	Valve position	Valve type*	FDA indication?†	Notes‡
Shelhigh	NR2000 Super Stentless	Aortic	Porcine	Unable to determine	
Shelhigh	NR900A	Tricuspid	Porcine	Unable to determine	
Shelhigh	Pulmonic Valve Conduit, No-React® Treated, Model NR-4000 Series	Pulmonary	Bovine & porcine	Yes (FDA)	FDA approved for use as humanitarian use devices under HDEs (FDA)
Sorin Biomedica Cardio	Pericarbon Freedom Solo	Aortic	Bovine pericardium	Unable to determine	
Sorin Biomedica Cardio	Pericarbon Freedom Stentless	Aortic	Bovine pericardium	Unable to determine	
Sorin Biomedica Cardio	Pericarbon More	Aortic & Mitral	Bovine pericardium	Unable to determine	
Sorin Biomedica Cardio	Soprano	Aortic	Bovine pericardium	Unable to determine	
St. Jude Medical	St. Jude Medical Biocor Porcine Stentless Bioprosthetic Heart Valve	Aortic	Porcine	Unable to determine	
St. Jude Medical	St. Jude Medical Biocor Valve and Biocor Supra Valve	Mitral & aortic	Porcine	Yes (FDA)	
St. Jude Medical	St. Jude Medical Epic Tissue Valve with Silzone Coating	Mitral & aortic	Porcine	Unable to determine	No longer marketed (non-FDA)
St. Jude Medical	St. Jude Medical Epic Valve and Epic Supra Valve	Aortic	Porcine	Yes (FDA)	Stented (non-FDA)
St. Jude Medical	St. Jude Medical Toronto SPV Valve [Stentless Porcine Aortic], Model SPA-101	Aortic	Porcine	Yes (FDA)	
Unknown	Ionescu-Shiley	Unknown	Bovine	Unable to determine	Stented (non-FDA)
Wessex Medical	Wessex	Unknown	Porcine	Unable to determine	Stented (non-FDA)

* Valve type for mechanical valves is either Caged-ball, Tilting disc, Bileaflet, or Unknown; and for bioprosthetic valves either Bovine, Equine, Porcine, Human, or Unknown.

† FDA indication column identifies the source of the FDA status as determined by the FDA (FDA) or a non-FDA source (non-FDA), or as Unable to determine.

‡ Notes column indicates the source of the note as determined by an FDA source (FDA) or a non-FDA source (non-FDA).

Table 2. Percutaneous heart valves in use or in development

Company	Valve name	Valve position	Valve type*	FDA indication?
CoreValve, Inc.	CoreValve Revalving System	Aortic	Porcine	No
Direct Flow Medical, Inc.	Direct Flow Medical Valve	Aortic	Equine	No
Edwards Lifesciences, LLC	Edwards SAPIEN, Cribier Edwards & Percutaneous Heart Valve Technologies	Aortic	Equine	No
Medtronic, Inc.	Melody Valve	Aortic	Bovine	No
Sadra Medical	Lotus Valve	Aortic	Bovine	No
Unknown	Paniagua Heart Valve	Aortic	Unknown	No

* Valve type for percutaneous valves is either Bovine, Equine, Porcine, Human, or Unknown.

Classes of Heart Valves

Diseased heart valves can be replaced with mechanical or biological valves. Mechanical valves employ caged-ball, tilting disc, and bileaflet designs. The first artificial heart valve was a caged-ball design which utilized a metal cage to house a silicone coated ball.[23] Tilting disc valves employ a disc, controlled by a metal strut, which opens and closes with each cardiac cycle. Bileaflet valves utilize two semicircular leaflets that rotate around struts attached to the valve housing. At least six companies manufacture tilting disc or bileaflet mechanical valves that are currently available in the U.S. market (Table 1).

Biological valves (bioprostheses or tissue valves) are classified into two major categories: xenografts that are made from bovine, porcine, or equine tissue; and homografts obtained from cadaveric donors. Xenografts may have a supporting frame (stent) or no supporting frame (stentless). Xenografts are much more readily available than homografts. We identified seven different manufacturers of FDA-indicated xenografts, including bovine, porcine, stented, and stentless models (Table 1).

Percutaneous heart valves are stent-based xenografts that are collapsed onto a catheter and are expanded at the time of implantation. Percutaneous valves are an emerging technology. We identified six manufacturers of percutaneous valves (Table 2); none of these valves is FDA approved.

Heart Valve Design

Replacement heart valves must be durable to minimize the risk of reoperation due to device failure. Factors that affect durability include: valve position; valve design; valve materials; and for bioprostheses, the processes used to fix tissue and to prevent calcification. A second goal is

to replicate natural valve function as closely as possible. Desirable functional characteristics are: a non-thrombotic surface; materials that do not predispose to endocarditis; and favorable hemodynamic profiles, including laminar flow, small transvalvular gradients, and minimal regurgitant volumes. One measure of hemodynamic efficiency is captured by the effective orifice area (EOA); larger EOAs provide better flow.

Advantages and Disadvantages of Different Heart Valves

Mechanical heart valves are more durable than bioprostheses and are readily available. Mechanical valves have a simple and standard implantation technique. However, mechanical valves require lifelong anticoagulation because of a greater risk of thrombosis. Anticoagulation increases the risk for bleeding and requires careful monitoring. Because of shear forces, mechanical valves may also cause hemolytic anemia. Mechanical valves are hemodynamically inefficient in smaller sizes, a limitation for aortic valve replacement in patients with a small aortic annulus. Caged-ball valves have the disadvantages of noise, hemodynamic inefficiency, and higher rates of thrombotic complications, necessitating a higher degree of anticoagulation than other mechanical valves.[8] Edwards Lifesciences discontinued production of the caged-ball valve in 2007. Tilting disc designs have superior hemodynamic efficiency to caged-ball designs but have the disadvantage of severe hemodynamic compromise if disc thrombosis or immobility occurs. Bileaflet mechanical valves have greater EOA than tilting disc valves and may be less thrombogenic than other mechanical valves. Because mechanical valves have the longest durability, they are recommended for younger patients (< 65 years old) who are willing to take oral blood thinners (e.g., warfarin) and participate in anticoagulation monitoring.[8]

Bioprosthetic heart valves (BHVs) are also readily available and do not require chronic

anticoagulation. BHVs have a simple and standard implantation technique and may have fewer infectious complications than mechanical valves. However, BHVs are less durable than mechanical valves. Structural deterioration is age-related, occurring more rapidly in younger age groups. Biological valves carry the theoretical risk of transmitting infection; at least one bovine valve has been recalled due to concern about transmission of bovine spongiform encephalopathy. Methods for tissue fixation and anticalcification have evolved since early BHVs. Second-generation BHVs are glutaraldehyde fixed under low pressure (compared to high pressure with the first generation), which is thought to increase durability. Stented bovine pericardial valves appear to have better hemodynamic performance and longer durability than stented porcine valves, especially in smaller sizes. Because stentless valves have less supporting material than stented bioprostheses, they have the potential for improved EOA and improved hemodynamic performance. Stentless valves may also be more durable than stented valves. However, stentless valves may be more technically difficult to implant, increasing operating room time and possibly surgical risk. An emerging technology is tissue-engineered valves using regeneration or repopulation approaches; no such FDA approved valves were identified.[24] Regeneration involves the implantation of a restorable matrix that is expected to remodel in vivo and yield a functional valve composed of the cells and connective tissue of the patient. Repopulation involves implanting a porcine or human valve that has been depopulated of native cells where the remaining scaffold of connective tissue is repopulated with the patient's own cells. The theoretical advantage is a living tissue that responds to growth and physiological forces in the same way a native valve does. The 2006 American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines recommend a bioprosthesis for patients of any age who will not take or have major contraindications to warfarin therapy, for patients ≥ 65 years of age who

do not have risk factors for thromboembolism, and for patients under age 65 who choose this approach for lifestyle reasons.[8]

The durability of homograft heart valves depends upon how the valve is recovered, processed, and preserved. Homograft aortic valves are supplied as a composite valve, aortic root, and part of the anterior mitral leaflet. This additional tissue is useful for severe disease due to endocarditis, and homografts are most frequently used for this indication. Durability of homografts does not appear to be superior to xenografts. Like xenografts, homograft (human) heart valves do not require chronic anticoagulation, risk of thromboembolism is very low, and these valves may be less likely to calcify than xenografts. Implantation procedures and reoperation for a failed valve are more complex than for standard mechanical or stented xenografts. The supply of homografts is much more limited than for mechanical valves or xenografts.

Valves inserted by a catheter have the potential advantage of lower perioperative morbidity and mortality than valves implanted using conventional surgical approaches. There are two catheter-based approaches, one that uses direct apical heart puncture, and a second using a percutaneous femoral approach. Neither approach requires cardiopulmonary bypass or a sternotomy, and the femoral approach may not require general anesthesia. The major theoretical advantages of the percutaneous approach are lower perioperative risk and less morbidity, leading to faster recovery times. Percutaneous valves have been used experimentally in patients deemed too high risk for conventional valve replacement surgery. Compared to valves implanted by open heart surgery, these valves are not sewn in, so there is an increased risk of migration. In addition, there are the risks associated with catheterization when the procedure is performed transfemorally. There is no long-term experience with these valves, so durability is uncertain

and the implantation approach is evolving. Percutaneous heart valves are not FDA approved, but at least one ongoing randomized trial is evaluating these valves.

Chapter 4. Studies Comparing Various Types of Conventional Heart Valves (Question 2)

Methods

Question

Question 2 was stated as follows: From a systematic literature scan of studies on different types of tissue and mechanical valves, describe the types of comparative studies, including basic study design, size of study, length of follow-up, and outcomes assessed. This literature scan will provide data to determine if a systematic review of this literature is possible and needed, and to provide needed context for understanding the evaluation and development of percutaneous heart valves.

Approach

For this question, we scanned the existing literature comparing different types of conventional (i.e., tissue and mechanical) heart valves in order to determine whether a systematic review of this literature is possible and needed, and to provide a context for understanding the development and evaluation of percutaneous heart valves. We sought to describe the available comparative studies in terms of the number of available studies, interventions compared, basic study design, size of study, length of follow-up, and outcomes assessed.

We began by searching for relevant, high-quality systematic reviews. We then expanded beyond these to a scan of available randomized controlled trials (RCTs) and select observational studies.

Literature Sources and Search Strategies

We used separate strategies to identify systematic reviews, RCTs, and observational studies, as follows:

- For potentially relevant ***systematic reviews,*** we searched PubMed® (1949 to October 17, 2008) using the detailed search strategy given in Appendix A. We also searched the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database using the terms "heart valve*" OR "heart valve prosthesis."
- We identified potentially relevant ***RCTs*** in two ways: (1) By reviewing the individual studies included in the systematic reviews that met our full-text inclusion criteria; and (2) by searching PubMed® (1949 to October 17, 2008) using the detailed search strategy given in Appendix A.
- We identified potentially important ***observational studies*** primarily by reviewing the individual studies included in the systematic reviews that met our full-text inclusion criteria. A few additional observational studies were picked up by the RCT search described in Appendix A. We also searched PubMed® (search date December 13, 2008) for recent (published during the past 5 years) observational studies that were large ($n \geq 1000$), *or* that had follow-up of 10 years or longer, *or* that evaluated valves not studied in RCTs using the detailed search strategy described in Appendix A.

Screening of Articles for Inclusion/Exclusion

Systematic reviews. Our search for systematic reviews identified a total of 325 citations. A single reviewer screened the titles and abstracts of all citations for potential inclusion. Articles

were included at this stage if they concerned conventional heart valves and appeared to be a review article.

Citations included at the title-and-abstract stage were independently reviewed in full-text form by two researchers who decided whether to include or exclude the article. Articles meeting the following criteria were **included** for data abstraction:

- The article really was a systematic review, defined as a review including both a Methods section describing a search strategy and analytic approach, and abstractions of primary literature; *and*
- The review directly compared two or more different types of conventional heart valves; *and*
- The review concerned valve replacement (rather than repair); *and*
- The review focused on adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- The review was published in English in the year 2000 or later.

When the two reviewers arrived at different conclusions about whether to include or exclude an article, they were asked to reconcile the difference.

Of the 325 potentially relevant citations identified, 283 were excluded at the title-and-abstract screening stage, leaving 42 articles to be reviewed in full-text form. Of these, 35 were excluded, and seven publications, describing six distinct systematic reviews, were included.

RCTs. Our search for RCTs identified 416 potentially eligible articles. The inclusion criteria applied at both the title-and-abstract and full-text screening stages were:

- Comparison of two or more heart valves for valve replacement (rather than repair); *and*
- Randomized allocation to treatment; *and*

- Study conducted in adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- Study published in English.

A single investigator screened titles and abstracts and full texts. If there was any uncertainty about whether an article should be included (e.g., if it was unclear whether allocation to treatment was truly randomized), a second investigator was consulted.

Of the 416 potentially relevant articles identified, 329 were excluded at the title-and-abstract screening stage, leaving 87 articles for full-text review. Of these, 77 articles, describing 57 separate RCTs, met our inclusion criteria and are described below. Only 16 of these were included in previous reviews.

Observational studies. Our search for observational studies identified 1160 potentially eligible articles. The inclusion criteria applied at both the title-and-abstract and full-text screening stage were:

- Observational study design; *and*
- Comparison of two or more heart valves for valve replacement (rather than repair); *and*
- Study population large (n ≥ 1000) *or* follow-up ≥ 10 years *or* study evaluated a valve not evaluated in RCTs; *and*
- Study conducted in adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- Study published in English.

A single investigator screened titles and abstracts and full texts. If there was any uncertainty about whether an article should be included, a second investigator was consulted.

Of the 1160 potentially relevant citations, screening of titles and abstracts excluded 1096,

leaving 64 for full-text review. Of these, 24 were excluded on full-text screening, leaving 40 included articles, each describing a unique study. Of these 40, 26 were included in the previous systematic reviews we identified and included.

Data Abstraction and Development of Evidence Tables and Other Summary Tables

The Duke research team developed data abstraction forms/evidence table templates for abstracting data for the various key questions (Appendix B). A pair of researchers was assigned to each key question to abstract data from the eligible articles. For Question 2, we completed detailed evidence tables only for the included systematic reviews (see Appendix C, Evidence Table 1). Data abstracted included the number and designs of included studies, patient descriptors, heart valves compared, and outcomes reported. One researcher abstracted the data, and a second over-read the article and the accompanying abstraction to check for accuracy and completeness.

For the RCTs and observational studies that met our inclusion criterion, we abstracted basic information on the interventions compared, study design, size of study, length of follow-up, and outcomes assessed into summary tables (Appendix D, Tables D-1 and D-2).

Quality Assessment Criteria

Systematic reviews. The methodological quality of the included systematic reviews was evaluated independently by two investigators using a quality assessment tool developed specifically for this project. This tool was adapted from a similar instrument used in a previous evidence report prepared for the Agency for Healthcare Research and Quality (AHRQ),[25] which

in turn was based on the Quality Of Reporting Of Meta-analyses (QUOROM) statement.[26]

The 10 quality criteria assessed were stated in question form; possible responses were "Yes," "Partially," "No," or "Can't tell." The criteria used (with notes on how to operationalize them in italics) were as follows:

1. Was a focused clinical question clearly stated?

   For "yes," should at least identify population and interventions; does not have to be in PICO format (Patient population, Intervention, Comparison, Outcomes).

2. Was the search for relevant studies detailed and exhaustive?

   Consider and rate two components: (a) Search methods described in enough detail to permit replication? (b) Databases and search terms appropriate? Consider any restrictions imposed (e.g., years, age groups, language).

3. Were inclusion/exclusion criteria clearly defined and appropriate?

   Consider and rate two components: (a) Were the criteria specified clearly enough to permit replication? (b) Were these criteria likely to capture all relevant studies? Consider criteria related to study population, intervention, outcomes, and study design.

4. Were the primary studies evaluated for quality, and were quality assessments done appropriately?

   Consider and rate two components: (a) Was study quality assessed? (b) Was quality assessment performed using a validated instrument?

5. Were assessments of studies reproducible?

   Consider and rate two components: (a) Did two or more independent raters abstract data? (b) Was an appropriate method used for resolving disagreements?

6. Were analyses conducted to measure variability in effect?

Consider and rate two components: (a) Was there a check for heterogeneity statistically or graphically? (b) Were possible sources of any observed heterogeneity explored (e.g., differences in study design or population)?

7. Were results combined appropriately?

   Was an accepted quantitative or qualitative method of pooling used?

8. Was publication bias assessed?

   Consider whether any of the following methods were employed: Funnel plots, test statistics, or search of trials registry for unpublished studies.

9. Were both benefits and harms assessed?
10. Were the author's conclusions supported by the data presented?

When the two investigators disagreed in their assessments, they met to reconcile the difference. Results of quality assessments for individual systematic reviews are reported in Evidence Table 1 (Appendix C).

RCTs and observational studies. The RCTs and observational studies reviewed for this question were not assessed for methodological quality.

Results

Scan of Systematic Reviews

Reviews identified. We identified six systematic reviews, described in seven publications, that addressed the comparative efficacy of various conventional prosthetic heart valves and met our other inclusion criteria.[27-33] Major characteristics of these reviews are summarized in Table 3, and a detailed abstraction of each review is provided in Evidence Table 1 (Appendix C). Only one of the included reviews[28] met all 10 of the quality assessment criteria we applied. Common

limitations of other reviews included: inadequate or poorly described search strategies (5 of 6 reviews); failure to assess the quality of primary studies (5 of 6); and failure to examine for publication bias (4 of 6).

Table 3. Characteristics of included systematic reviews

Review	Included study designs	Numbers of studies and subjects	Valve comparison	Main outcomes reported
Kassai et al., 2000[27]	RCT	2 studies 1011 subjects	Aortic and/or mitral: Mechanical vs. bioprosthetic	Mortality, reoperation, bleeding
Kunadian et al., 2007[28]	RCT	11 studies 919 subjects	Aortic: Stented vs. non-stented bioprosthetic	Left ventricular mass regression, surgical procedure times
Lund and Bland, 2006[29]	Observational	38 studies 17,439 subjects	Aortic: Mechanical vs. bioprosthetic	Mortality
Puvimanasinghe et al., 2004[30] and Puvimanasinghe et al., 2003[31]	Observational	22 studies 13,281 subjects	Aortic: St. Jude mechanical vs. porcine bioprosthetic	Life expectancy, thrombotic and bleeding complications
Puvimanasinghe et al., 2006[32]	Observational	13 studies 6481 subjects	Aortic: Carpentier-Edwards pericardial aortic vs. Carpentier-Edwards suprannular bioprosthetic	Life expectancy, thrombotic and bleeding complications
Rizzoli et al., 2004[33]	Observational	11 studies 1160 subjects	Tricuspid: Bioprosthetic vs. mechanical valves	Survival, reoperation

Abbreviations: RCT = randomized controlled trial.

The included reviews are described in greater detail below, organized by valve comparison.

Mechanical versus bioprosthetic valves. Four systematic reviews, described in five papers,[27, 29-31, 33] compared mechanical and bioprosthetic valves. Kassai et al.[27] identified two RCTs in adults (n = 1011) and one in children (n = 218) comparing mechanical to bioprosthetic valves in aortic or mitral valve position. Specific valves compared were the Bjork-Shiley or

Lillehei-Kaster mechanical valves; and the Hancock, Carpentier-Edwards, or Angell-Shiley bioprosthetic valves. These valves are no longer in widespread use. Meta-analysis of the three trials showed no difference between mechanical and bioprosthetic valves for all-cause mortality at 5 years (relative risk [RR] 1.16, 95 percent confidence interval [CI] 0.97 to 1.39) or at 11 years (RR 0.94, 95 percent CI 0.84 to 1.06). Subjects receiving mechanical valves were less likely to undergo reoperation at 11 years (RR 0.4, 95 percent CI 0.29 to 0.58; x^2 for heterogeneity, p = 0.059), and less likely to have endocarditis (RR 0.6, 95 percent CI 0.3 to 0.95; x^2 for heterogeneity, p = 0.0001), but were more likely to have a bleeding complication (RR 1.65, 95 percent CI 1.26 to 2.18). A major limitation of this review is that the search only went through 1997.

A more recent systematic review[29] also compared mechanical and bioprosthetic valves in the aortic position, limiting the literature to observational studies with at least 10 years of patient follow-up. The review identified 32 articles describing 38 case series and reporting outcomes in 17,439 patients. Studies with more than 10 percent obsolete valve types and studies that did not report mortality outcomes were excluded. Valves compared were the St. Jude bileaflet disc, Carobmedics, Sorin bileaflet and single disc, ATS, On-X, Edwards Mira, Edwards Duromedics, Tekna valve, or Medtronic-Hall tilting disc mechanical valves; and the Carpentier-Edwards Perimount pericardial, Carpentier-Edwards porcine standard, Carpentier-Edwards porcine supra-annular, Hancock II and MO porcine, Sorin Mitroflow pericardial, Medtronic Mosaic, Edwards Prima stentles, St. Jude x-cell and Biocor porcine bioprosthetic valves. Statistical analysis using regression approaches showed no difference in mortality after adjusting for age, New York Heart Association (NYHA) class and presence of aortic regurgitation (0.23 fewer deaths per 100 patient-years with bioprosthetic valves; 95 percent CI -0.99 to 0.63). The advantage of this

review is that it focuses on studies describing real-world experiences with currently used valves. However, an important limitation is the reliance on case-series that do not directly compare mechanical to bioprosthetic valves. Indirect comparisons are more subject to bias and provide lower quality evidence.

Rizzoli et al.[33] reviewed the outcomes for mechanical versus bioprosthetic valves implanted in the tricuspid position. Eleven studies reporting "intra-institutional comparisons" of mechanical (n = 646) versus biological (n = 514) valves were included. Specific study designs and valve types were not described, but a review of the primary literature cited showed these to be observational studies. Median duration of follow-up was 6.5 years. In seven studies reporting mortality, the hazard ratio was 1.07 (95 percent CI 0.84 to 1.35), indicating a small, statistically non-significant increase for mechanical versus bioprosthetic valves. For three studies reporting freedom from reoperation, the pooled hazard ratio was 1.24 (95 percent CI 0.67 to 2.31) for mechanical versus bioprosthetic valves. There are a number of limitations to this review, including: primary data from observational studies that are at increased risk for bias; lack of quality assessments for the primary data; and no evaluation for publication bias. Observational studies are at risk for confounding by indication, with particular valves being selected based on clinical indications, leading to important baseline imbalances in prognostic factors between the mechanical and bioprosthetic groups.

A 2004 review and microsimulation described in two publications compared selected bileaflet mechanical valves and stented porcine bioprosthesis in the aortic position.[30, 31] Specific mechanical valves considered were the St. Jude Medical bileaflet valves-standard and haemodynamic plus models; bioprosthetic valves were Carpentier-Edwards-standard and supra-annular valves, Hancock-standard and modified orifice, and Hancock II valves. Studies in adult

populations with predominately first-time aortic valve replacement, valve events ascertained using standard definitions, and international normalized ratio values between 1.8 and 4.5 were included for review. Nine observational studies on St. Jude Medical valves and 13 studies on stented porcine bioprosthesis met inclusion criteria from the 144 identified in the search. Most of the 22 included studies were case series; 15 were retrospective designs, 5 were prospective, and 2 were not described. Meta-analysis showed the following event rates per 100 patient-years for mechanical versus bioprosthetic valves: valve thrombosis (0.16 vs. 0.01); thromboembolism (1.6 vs. 1.3); hemorrhage (1.6 vs. 0.4); and endocarditis (3.9 vs. 3.2 in first 6 months). Incorporating these estimates into a microsimulation model for a 65-year-old man, life expectancy was projected at 10.4 years for mechanical versus 10.7 years for bioprosthesis. Study limitations include: primary literature is predominately case-series; lack of assessment for study quality; a poorly described search strategy; and life expectancy results that depend on valid modeling.

In summary, two RCTs in adults showed no difference between mechanical and bioprosthetic valves in the aortic or mitral positions. However, the specific valves tested in these RCTs have been replaced by new models that may perform differently, and the study populations differ substantially from adults most commonly undergoing valve replacement today. In addition, standards for anticoagulation have changed to a lower international normalized ratio range, such that bleeding complications would now be expected to be lower. A large body of observational studies describing experiences with heart valve replacement has been summarized in systematic reviews. Although observational studies are at greater risk for bias than RCTs, and the systematic reviews evaluating them are of low to moderate quality, findings from those reviews are consistent with the findings from systematic reviews of RCTs.

Stented versus stentless bioprosthetic valves. Left ventricular hypertrophy is a complication of aortic stenosis, and maximizing hemodynamic results from aortic valve replacement is theorized to facilitate left ventricular mass regression and improve clinical outcomes. Stentless valves are xenografts that have no additional structure (stent) allowing for larger valve sizes to be implanted, maximizing the effective orifice area-to-tissue annulus ratio. Maximizing this ratio offers the potential for improved hemodynamic and clinical outcomes.

Only one systematic review evaluated stented versus stentless bioprosthetic valves.[28] This high-quality review included 11 RCTs of aortic valve replacement conducted in Western Europe and Canada and reported between 1996 and 2006. A total of 445 subjects were randomized to stented valves: Carpentier Edwards Perimount, More, Mosaic, Intact, and Hancock II. The Prima Plus, Freedom, Freestyle and Toronto Stentless valves were implanted in 474 subjects. Six studies (n = 599) reported the primary outcome left ventricular mass index (LVMI) at 6 months, and 5 studies (n = 550) reported this outcome at 12 months or later. LVMI was lower for stentless valves at 6 months (weighted mean difference [WMD] -6.42, 95 percent CI -11.63 to -1.21), but this improvement disappeared after 12 months (WMD 1.19, 95 percent CI -4.15 to 6.53), and the meta-analysis showed significant heterogeneity that could not be explained by subgroup analyses. Secondary outcomes showed improved hemodynamic results for stentless valves (mean aortic gradient, WMD -3.57 mm Hg, 95 percent CI -4.36 to -2.78; peak aortic gradient, WMD -5.80, 95 percent CI -6.90 to -4.69), but longer operative cross-clamp time (WMD 23.5 minutes greater, 95 percent CI 20.4 to 26.1) and bypass time (WMD 29, 95 percent CI 24.4 to 34.0). There was no difference in mortality for stentless versus stented valves at 1-year follow-up (odds ratio [OR] 0.91, 95 percent CI 0.52 to 1.57).

The primary limitations of this review are the short follow-up duration, the lack of symptom

or functional status outcomes, and the significant unexplained heterogeneity across studies. These short-term studies suggest tradeoffs – improved hemodynamics at the expense of longer procedure times for stentless valves – and no evidence for improved cardiac function or lower mortality for stentless versus stented valves at 12 months.

Comparisons of one bioprosthetic valve versus another. A 2006 review and microsimulation[32] compared two bioprosthetic valves, the Carpentier-Edwards pericardial valve and the Carpentier-Edwards supraannular valve, both in the aortic position. These "second generation" valves were introduced in the 1980s and incorporated improvements in valve design aimed at reducing structural valvular deterioration and improving hemodynamic performance. The review included studies that focused on patients aged > 15 years with predominately first time aortic valve replacement. Additional inclusion criteria were: patients who predominately did not require long-term anticoagulation; valve sizes 19-31 mm; and valve events ascertained using standard definitions. Eight observational studies (n = 2685) on pericardial valves and five studies (n = 3796) on supraannular valves met the inclusion criteria from the 48 identified in the search. Only two of these studies directly compared the two types of valves; the remaining 11 were case series of a single valve type. Meta-analysis of data from all included studies showed the following event rates per 100 patient years for Carpentier-Edwards pericardial versus Carpentier-Edwards supraannular: valve thrombosis (0.03 vs. 0.02); thromboembolism (1.35 vs. 1.76); hemorrhage (0.43 vs. 0.46); endocarditis (0.62 vs. 0.39); and non-structural dysfunction (0.13 vs. 0.61). Neither CIs nor p-values were given for these comparisons. Incorporating these estimates into a microsimulation model for a 65-year-old man, life expectancy was projected at 10.8 years for the Carpentier-Edwards pericardial valve versus 10.9 years for the Carpentier-Edwards supraannular valve. This review and microsimulation are strengthened by model

estimates from observational studies with long follow-up periods cited by the review authors. As in other reviews that rely on observational studies, indirect comparisons and confounding by indication may bias outcome estimates. In addition, the systematic review methods are poorly described, decreasing confidence in the estimates used in the microsimulation model.

Scan of Randomized Controlled Trials

As described in the Methods section, above, in order to supplement the information obtained from systematic reviews, we sought to identify additional relevant RCTs and large observational studies that compared two or more conventional heart valves. For each such study we abstracted key design features to inform a judgment about the feasibility and possible value of conducting a systematic review of this literature.

We identified 57 unique RCTs, involving 13,379 subjects, that met our inclusion criteria (see Appendix D, Table D-1). Sixteen of these trials were included in the systematic reviews described above. The 57 trials evaluated valve replacement in the aortic position (n = 43), aortic and/or mitral position (n = 11), or mitral position alone (n = 3). For the 43 studies exclusively evaluating aortic valve replacement, the most common comparison was of bioprosthetic stented versus bioprosthetic stentless valves (Table 4). For the 11 studies evaluating aortic and/or mitral valve replacement, comparisons were: homograft versus mechanical (n = 1); one mechanical valve versus another (n = 7); mechanical versus bioprosthetic (n = 2); and one bioprosthetic valve versus another (n = 1). The three studies of mitral valve replacement all compared mechanical valves.

Table 4. Types of valves compared in the aortic position – randomized controlled trials*

	Homograft	Autograft	Mechanical	BP-stented	BP-stentless
Homograft	0	3	0	1	3
Autograft	-	0	1	0	0
Mechanical	-	-	12	2	2
BP-stented	-	-	-	7	15
BP-stentless	-	-	-	-	1

* Number of studies is given for each comparison. The total number of comparisons exceeds the number of studies because some studies included more than one comparison.

Abbreviations: BP = bioprosthetic.

Within these major classes of valve types, the number of unique valves evaluated was large (Table 5). Valve technology has evolved, and some of these valves are no longer marketed in the United States. Some valves are designed for special purposes, such as a lower profile for a small annulus. A systematic review would need to carefully evaluate whether valves in a general class (e.g., mechanical) could be considered together for analytic purposes.

Table 5. Conventional valves evaluated in randomized controlled trials

Mechanical	Bioprosthetic-stented	Bioprosthetic-stentless
Aortec Ultracor	Carpentier-Edwards Pericardial	Carpentier Edwards Prima Plus
ATS Medical Bioflow	Carpentier-Edwards Perimount	Cryolife O'Brien Model 300*
Bjork-Shiley Monostrut*	Carpentier-Edwards Perimount Magna	Medtronic Freestyle
Bjork-Shiley Low Profile*	Medtronic Hall Hancock II	Sorin Freedom
Bjork-Shiley Convex/Concave*	Medtronic Mosaic	Biocor
Carbomedics (unspecified)	Hancock standard*	St. Jude Toronto
Carbomedics Reduced bileaflet	Sorin More	
Edwards Duromedics		
Edwards Mira		
Lillehei-Kaster*		
Lillehie-Kaster Low Profile*		
OnX		
Medtronic Hall		
Medtronic Advantage Supra		
Sorin Slimline		
St. Jude Hemodynamic Plus		
St. Jude High Performance		
St. Jude Regent		
St. Jude Silzone*		

Mechanical	Bioprosthetic-stented	Bioprosthetic-stentless
Starr Edwards		

* No longer commercially available.

Other critical issues affecting the feasibility of a systematic review are the timing, types, and quality of outcomes reported. Long-term studies are important to adequately evaluate mortality, reoperation for structural device failure, and long-term adverse effects such as stroke and bleeding complications. For the 42 studies of aortic valve replacement, outcomes were reported at 1 year or sooner in 29 studies (69 percent), > 1 to 5 years in 10 studies (24 percent), and > 5 to 10 years in 3 studies (7 percent). Studies of aortic and/or mitral replacement generally had longer follow-up: > 1 to 5 years for 4 studies (36 percent); > 5 to 10 years for 5 studies (45 percent); and > 10 years for 2 studies (18 percent). Mean follow-up for the three mitral valve studies was about 5 years. The types of outcomes reported are summarized in Table 6. Intermediate outcomes such as hemodynamic changes were the most commonly reported. Although adverse effects were reported in about three-quarters of studies, we identified considerable heterogeneity in reporting, making a valid summary estimate more difficult.

Table 6. Number of randomized controlled trials reporting various outcomes

Outcomes	Aortic (n = 43)	Aortic/Mitral (n = 11)	Mitral (n = 3)
Mortality	33	9	3
Clinical	22	7	3
Hemodynamic	39	2	2
Cardiac function	36	1	1
Reoperation	12	9	3
Adverse effects	29	10	3

Scan of Observational Studies

We identified 40 unique observational studies, involving 332,551 subjects, that met our inclusion criteria (see Appendix D, Table D-2). Twenty-six of these studies had been included in the systematic reviews described above. A single Medicare claims study accounts for 307,054 of the subjects.[34] Studies evaluated valve replacement in the aortic position (n = 22), aortic and/or

other valve positions (n = 5), tricuspid position (n = 10), and mitral position (n = 2); one study did not report valve position. For the 27 studies evaluating aortic and/or other valve replacements, mechanical versus bioprosthetic stented and bioprosthetic stented versus bioprosthetic stentless were the most common comparisons, followed by comparisons of two bioprosthetic stented valves (Table 7). Of the 10 studies evaluating tricuspid valve replacement, nine compared mechanical to stented bioprosthesis.

Table 7. Types of valves compared in the aortic and/or other position*

	Homograft	Autograft	Mechanical	BP-stented	BP-stentless	BP-mixed
Homograft	0	0	0	2	0	0
Autograft	-	0	0	0	0	0
Mechanical	-	-	3	7	0	1
BP-stented	-	-	-	5	7	0
BP-stentless	-	-	-	-	1	0
BP-mixed	-	-	-	-	-	0

* Number of studies is given for each comparison. Two studies that did not specify the type of bioprosthetic valve (stented vs. stentless) are omitted.[34, 35] The total number of comparisons exceeds the number of studies because some studies made more than one comparison.

Abbreviations: BP = bioprosthetic.

Thirty-six different named valves are evaluated in these studies, including 21 valves not evaluated in RCTs (Table 8).

Table 8. Conventional valves evaluated in observational studies

Mechanical	Bioprosthetic-stented	Bioprosthetic-stentless
Aortec Ultracor	Biocor porcine	Carpentier Edwards Prima
ATS Medical Bioflow	Carpentier-Edwards Perimount	Medtronic Freestyle
Bjork-Shiley Monostrut*	Carpentier-Edwards porcine	Shelhigh Super stentless
Carbomedics (unspecified)	Hancock Standard*	St. Jude Toronto
Debakey	Ionescu-Shiley bovine	
Edwards Duromedics	Medtronic Intact	
Edwards Tekna	Medtronic Mosaic	
Hall-Kaster	Mitroflow	
Harken	Sorin Pericarbon	
OnX	Wessex Medical porcine	

Mechanical	Bioprosthetic-stented	Bioprosthetic-stentless
Medtronic Hall		
Omniscience		
Smelloff-Cutter		
Sorin Allcarbon		
Sorin Bicarbon		
Sorin Carbocast		
Sorin Monocast		
Sorin Monodisc		
St. Jude Medical		
St. Jude High Peformance		
St. Jude Regent		
Starr Edwards*		

* No longer commercially available.

Compared to RCTs, observational studies are more likely to describe longer follow-up and report clinically important outcomes. Twenty-six of the 41 included studies (63 percent) had a mean follow-up duration exceeding 5 years. Most studies reported mortality rates, adverse effects, and reoperation rates (Table 9). A complicating issue for a possible systematic review is variability across studies in potential confounders controlled for in the analyses.

Table 9. Number of observational studies reporting various outcomes*

Outcomes	Aortic/Other (n = 27)	Tricuspid (n = 10)	Mitral (n = 2)
Mortality	22	10	1
Clinical	5	3	0
Hemodynamic	9	0	0
Cardiac function	9	0	0
Reoperation	17	8	1
Adverse effects	19	8	2

* One study that did not specify valve position is omitted.[36]

Summary

Our literature scan identified six relevant systematic reviews, one of high quality, and a large

body of RCTs and observational studies comparing different conventional heart valves with one another. The single high-quality meta-analysis evaluated 11 studies comparing stented to stentless bioprosthetic valves; we identified an additional four relevant trials and seven observational studies. There is sufficient literature to address other relevant comparisons, such as between mechanical and bioprosthetic valves, and between homografts and bioprosthetic valves, and to make selected within-class comparisons (e.g., among differing mechanical valves).

Based on varying duration of follow-up and types of outcomes reported, a systematic review would need to evaluate both RCTs and observational studies. RCTs of currently available valves tend to have shorter follow-up and thus are unable to evaluate critical outcomes such as reoperation for valve failure, late adverse effects, and long-term survival. Observational studies with longer-term follow-up can supplement findings from randomized trials. Systematic reviews will be complicated by heterogeneity in study design, valve position, and valve types. Other challenges include: whether to include studies of valves no longer marketed that may perform differently from modern valves; accounting for changes in anticoagulation targets and thus the risk for bleeding; and accounting for observational studies that vary by whether outcomes are adjusted for potential confounders. A systematic review that carefully develops a conceptual framework and evaluates the association between intermediate outcomes such as hemodynamic changes and long-term patient important outcomes would be particularly useful.

Chapter 5. Studies of Percutaneous Heart Valves (Question 3)

Methods

Question

Question 3 was stated as follows: From a systematic literature scan of studies on different types of percutaneous heart valves, provide a synthesis of the following variables:

a. Number for each type of valve.
b. Type of studies – comparative and non-comparative randomized controlled trials (RCTs), non-randomized controlled clinical trials (CCTs), case series, etc.
c. Variables associated with surgery (implantation technique), setting, etc.
d. Size of studies/length of follow-up.
e. Patient population/concurrent and prior treatments.
f. Hemodynamic success rates reported.
g. Harms reported.

Approach

We scanned the existing published and gray literature on different types of percutaneous heart valves in order to synthesize information on the variables specified in Question 3. We limited our search to human studies of percutaneous heart valves in adults.

Literature Sources and Search Strategies

We searched PubMed® and EMBASE® (both through December 31, 2008) for relevant published studies using the detailed search strategies given in Appendix A.

We also conducted an extensive search of the gray literature for this question (search last updated January 1, 2009). We were assisted in this effort by a librarian with expertise in gray literature searching, who suggested sources and search terms. The gray literature sources consulted, search terms used, and results are described in Table 10.

Table 10. Percutaneous heart valves – gray literature sources, search terms, and results

Source	Search term(s)	Restrictions	Number of citations identified	Number of eligible studies
General gray literature sources				
Google Scholar (http://scholar.google.com/) Advanced Scholar Search: http://scholar.google.com/advanced_scholar_search?hl=en&lr=	All of the words: "percutaneous," "heart," and "valve"	• In the title of the article • In the "Medicine, Pharmacology, and Veterinary Science" subject area • Published 2003-2008	56	0
CRISP (Computer Retrieval of Information on Scientific Projects; http://crisp.cit.nih.gov/) Query Form: http://crisp.cit.nih.gov/crisp/crisp_query.generate_screen	"percutaneous" AND "valve"	• All award types • All IRGs • All institutes and centers • Fiscal years 2003-2008	12	0
The New York Academy of Medicine Grey Literature Report (http://www.nyam.org/library/pages/grey_literature_report) Search under "Search the Grey Literature Collection"	Subject Keyword "heart valve" anywhere in text or title	None	37	0
OAIster (University of Michigan - collection of free, otherwise difficult-to-access resources from 327 institutions; http://www.oaister.org/) Search page (http://quod.lib.umich.edu/cgi/b/bib/bib-idx?c=oaister;page=simple)	"percutaneous" AND "heart" AND "valve"	None	58	0
NICHSR (National Library of Medicine, National Information Center of Health Services Research and Health Care Technology (http://wwwcf.nlm.nih.gov/hsr_project/home_proj.cfm)	"percutaneous"	None	15	0
WHO Publications (http://www.who.int/publications/en/)	"percutaneous heart valve"	None	69	0
Abstracts from scientific meetings				
American Heart Association (AHA;	All of the words:	• In title or abstract	30	1

Source	Search term(s)	Restrictions	Number of citations identified	Number of eligible studies
http://scientificsessions.americanheart.org/portal/scientificsessions/ss/); Advanced Search: http://circ.ahajournals.org/search.dtl	"percutaneous," "heart," and "valve"	• Include AHA Scientific Sessions Abstracts • 2003-2008		
American Cardiology Association (ACC; http://www.acc.org/) Search page: http://content.onlinejacc.org/search.dtl	All of the words: "percutaneous," "heart," and "valve"	• In title or abstract • All JACC journals • 2003-2008	10	0
Transcatheter Cardiovascular Therapeutics (TCT) Abstracts 2008 meeting Search page: http://www.aievolution.com/tct0801/	"percutaneous heart valve"	All abstract categories	0	0
	"percutaneous" "transapical" "transcatheter"	All abstract categories	211 (percuta-neous) 3 (transapical) 15 (trans-catheter)	7
European Society of Cardiology (ESC) http://www.escardio.org/Pages/index.aspx) Search page: http://spo.escardio.org/abstract-book/topic.aspx	Browsed "surgery and intervention in valve disease" topic	ESC Congress 2007 or ESC Congress 2008	13 (2007) 16 (2008)	1 (2 abstracts)
American Association of Thoracic Surgery (AATS) http://www.aats.org/multimedia/files/AnnualMeeting/2008/AATS08-Final-Program.pdf	Browsed (not possible to search using keywords/subject terms)	AATS Annual Meetings 2007 and 2008	NA	2
Society of Thoracic Surgeons (STS) http://www.sts.org/	Transcatheter Percutaneous Transapical	STS Annual Meeting 2008	NA	0

Source	Search term(s)	Restrictions	Number of citations identified	Number of eligible studies
Ongoing trials				
ClinicalTrials.gov (http://www.clinicaltrials.gov/) Basic Search: http://www.clinicaltrials.gov/ct2/search	(percutaneous OR transapical) AND (heart OR valve)	None	17	4

Finally, colleagues working in AHRQ's Effective Health Care Program at Oregon Health & Science University contacted companies known or believed to manufacture percutaneous heart valves on our behalf to request any additional information they wished to submit in the form of "Scientific Information Packets." The text of the form letter used for this purpose is provided in Appendix E. Requests to companies were sent out on August 5, 2008; the deadline for responding was September 16, 2008. Table 11 provides a list of the companies contacted and their responses.

Table 11. Requests for Scientific Information Packets and responses from companies

Company	Response
Cardiac Dimensions	Telephone response on 5 August 2008 – nothing to submit
CoreValve, Inc.	No response
Direct Flow Medical, Inc.	No response
Edwards Lifesciences, LLC	Hardcopy Scientific Information Packet received 16 September 2008
Endoluminal	Unable to contact; no contact information available from any source, may no longer be a company
Endovalve	No response
Evalve, Inc.	E-mail dated 7 August 2008 – nothing to submit
Hansen Medical	E-mail dated 6 August 2008 – nothing to submit
JenaValve Technology, Inc.	No response
Medtronic, Inc.	E-mail dated 29 August 2008 – nothing to submit
MiCardia	E-mail dated 5 August 2008 – nothing to submit
Mitralign, Inc.	No response
Myocor, Inc.	No response
Sadra Medical	No response
Viacor, Inc.	E-mail dated 5 August 2008 – nothing to submit

Screening for Inclusion/Exclusion

Published studies. Citations to published studies retrieved through searches of PubMed® and EMBASE® were supplemented by information provided in the Scientific Information Packet submitted by Edwards Lifesciences, LLC. A single reviewer screened the titles and

abstracts of all citations for potential inclusion. All citations that appeared to report primary data on studies of percutaneous heart valves in humans were included at this stage, with no limit by language or heart valve position (e.g., aortic vs. mitral).

Citations included at the title-and-abstract stage were independently reviewed in full-text form by two researchers who decided whether to include or exclude the article. Articles meeting the following criteria were **included** for data abstraction:

- Interventions included percutaneous heart valves; *and*
- Study involved valve replacement (rather than repair); *and*
- Primary data were reported; *and*
- Study was conducted in humans; *and*
- Study was conducted in adults (all patients ≥ 18 years of age or, if mixed population, then either 80 percent adults or results reported separately for adults); *and*
- At least one clinical outcome was reported (e.g., mortality, hemodynamic parameters of success, successful implantation rates); *and*
- Study was published in English.

Note that no restrictions were imposed regarding:

- Study design (all designs acceptable); *or*
- Sample size (n ≥ 1 acceptable).

When the two reviewers arrived at different conclusions about whether to include or exclude an article, they were asked to reconcile the difference.

A total of 42 published reports were screened at the full-text stage. Of these, 10 were excluded, and 32 were included.

Gray literature – general sources. A single investigator searched the general gray literature sources listed in Table 10 and screened the material identified for potential relevance using the inclusion/exclusion criteria described above for published studies. No additional relevant studies were identified.

Gray literature – meeting abstracts. A single investigator searched the sources listed in Table 10 for potentially relevant abstracts from recent scientific meetings. Titles and abstracts were screened online, and potentially relevant abstracts were then reviewed in full using the inclusion/exclusion criteria described above for published studies. Abstracts meeting the inclusion criteria were further screened to eliminate those abstracts that duplicated information reported more fully in published studies. Twelve meeting abstracts describing 11 separate studies were finally included.

Gray literature – ongoing studies. A single investigator searched ClinicalTrials.gov for potentially relevant ongoing studies of percutaneous heart valves. Four relevant trials were identified.

Registries of percutaneous heart valve implantation. The Scientific Information Packet provided by Edwards Lifesciences, LLC, also included information on four relevant registries of percutaneous heart valve implantation.

Data Abstraction and Development of Evidence Tables and other Summary Tables

The Duke research team developed data abstraction forms/evidence table templates for abstracting data for the various key questions (Appendix B). A pair of researchers was assigned to each key question to abstract data from the eligible articles. For Question 3, we created

evidence tables only for published studies (see Appendix C, Evidence Table 2). Data abstracted from these studies included: date of publication; country; study design; study objectives; duration of follow-up; number, age, and sex of participants; indication for percutaneous heart valve; valve name; size of catheter; implementation approach; implantation rates; and clinical outcomes, including hemodynamic measurements and 30-day mortality rates, complications, and device dysfunction rates. One researcher abstracted the data, and a second over-read the article and the accompanying abstraction to check for accuracy and completeness.

Important data from the included meeting abstracts, ongoing trials, and registries were abstracted into summary tables included below, under Results.

Statistical Analysis

Descriptive statistics are used to summarize and analyze the data abstracted from the fully published reports, as is appropriate for a horizon scan of a literature comprised solely of non-comparative studies.

Quality Assessment Criteria

The studies included for this question were not formally assessed for methodological quality.

Results

Studies Identified

We identified 26 fully published studies, described in 32 publications, that assessed the feasibility and short-term safety of implanting percutaneous heart valves and met our other inclusion criteria.[37-68] These reports are summarized in Table 12 and Table 13. A total of 542

unique patients are represented in these 32 publications. Detailed abstractions of the included studies are provided in Evidence Table 2 (see Appendix C).

Our gray literature scan identified 12 scientific meeting abstracts that presented data on 11 studies not described in the published reports.[69-80] These abstracts, which are summarized in Table 14, report data on 923 patients who have undergone percutaneous heart valve replacement. Insufficient evidence was reported in the abstracts to make it possible to determine fully how many patients may be represented in more than one abstract, or in both an abstract and a fully published report.

Finally, we identified four ongoing clinical trials via the website www.clinicaltrials.gov (Table 15) and four registries (Table 16).

Results from Published Studies

Table 12, Table 13, and the paragraphs below summarize the most important findings from our scan of published studies. Data presented at scientific meetings but not yet published in peer-reviewed journals are not included in the following information synthesis for the following reasons: (1) meeting abstracts usually contain insufficient information to create sufficiently detailed evidence tables; (2) data presented at scientific meetings often differ from those that later appear in published reports, thereby putting into question the accuracy of the data presented in the abstracts; and (3) information presented at meetings is often derived from a subset of patients whose data have undergone only preliminary analysis.

Table 12. Summary of published studies of percutaneous heart valve implantation

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Follow-up (months)	Clinical indication	Successful implantation rate	Approach	Catheter size	30-day survival
Edwards Lifesciences, LLC								
Cribier et al., 2004[39] Eltchaninoff et al., 2002[38] Cribier et al., 2002[37]	Percutaneous Heart Valve	6 1 (0) 1 (0)	3	Aortic stenosis	5/6 (83%)	Antegrade	24 Fr	3/6 (50%)
Bauer et al., 2004[40]	Percutaneous Heart Valve	8	1	Aortic stenosis	8/8 (100%)	Antegrade (n = 6) Retrograde (n = 2)	NR	5/8 (63%)
Hanzel et al., 2005[41]	Percutaneous Heart Valve	1	5 days	Aortic stenosis	1/1 (100%)	Aborted antegrade to retrograde	24 Fr	NR
Cribier et al., 2006[42]	Percutaneous Heart Valve	35 (33)[a]	26	Aortic stenosis	27/35 (77%)	Antegrade (n = 26) Retrograde (n = 7) Aborted retrograde to antegrade (n = 1) Aborted procedures (n = 1)	NR	21/36 (58%)
Chandavimol et al., 2006[43]	Percutaneous Heart Valve	1	12	Aortic stenosis	1/1 (100%)	Retrograde	24 Fr	1/1 (100%)
Webb et al., 2007[44] Webb et al., 2006[45]	Cribier Edwards Cribier	50 18 (0)	12	Aortic stenosis	43/50 (86%)	Retrograde	NR	44/50 (88%)
Lichtenstein et al., 2006[46] Ye et al., 2007[47]	Cribier-Edwards Cribier-Edwards	7 7 (0)	6	Aortic stenosis	7/7 (100%)	Transapical	NA	6/7 (86%)
Walther et al., 2008[48] Walther et al., 2007[49]	Edwards SAPIEN THV Cribier-Edwards	59 30 (0)[b]	3	Aortic stenosis	55/59 (93%)	Transapical	NA	51/59 (86%)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Follow-up (months)	Clinical indication	Successful implantation rate	Approach	Catheter size	30-day survival
Walther et al., 2008[50]	Edwards SAPIEN THV	50 (20)[b]	18	Aortic stenosis	50/50 (100%)	Transapical	NA	46/50 (92%)
Zierer et al., 2008[51]	Edwards SAPIEN THV	26	1	Aortic stenosis	25/26 (96%)	Transapical	NA	22/26 (85%)
Svensson et al., 2008[52]	Edwards	40	11	Aortic stenosis	35/40 (88%)	Transapical	NA	33/40 (83%)
Rodes-Cabau et al., 2008[53]	Edwards-Sapien	22	> 6	Aortic stenosis	21/23 (91%) (2 procedures in 1 patient)	Retrograde (n = 10) Transapical (n = 11) Aborted retrograde to antegrade (n = 1)	24 Fr (n = 10) 22 Fr (n = 12)	20/22 (91%)
Totals: Edwards Lifesciences, LLC		**273**			**278/306 (91%)** **(32 patients counted twice, and 1 patient with 2 procedures)**	**Antegrade (n = 36)** **Retrograde (n = 70)** **Transapical (n = 163)** **Aborted antegrade to retrograde (n = 1)** **Aborted retrograde to antegrade (n = 2)** **Aborted procedure (n = 1)**		**252/305 (82%)** **(32 patients counted twice)**
CoreValve ReValving System								
Grube et al., 2005[54]	CoreValve Revalving System	1	0.5	Aortic stenosis	1/1 (100%)	Retrograde	25 Fr	1/1 (100%)
Grube et al., 2006[55]	CoreValve Revalving System	25	12	Aortic stenosis	22/25 (88%)	Retrograde	24 Fr (n = 10) 21 Fr (n = 15)	20/25 (80%)
Grube et al., 2007[56]	CoreValve Revalving System	86 (76)[c]	> 1	Aortic stenosis	76/86 (88%)	Retrograde	21 Fr (n = 50) 18 Fr (n = 36)	76/86 (88%)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Follow-up (months)	Clinical indication	Successful implantation rate	Approach	Catheter size	30-day survival
Grube et al., 2008[57]	CoreValve Revalving System	136 (122)[c]	> 12	Aortic stenosis	Generation 1: 7/10 (70%) Generation 2: 17/24 (71%) Generation 3: 93/102 (92%)	Retrograde	25 Fr (n = 10) 21 Fr (n = 24) 18 Fr (n = 102)	Generation 1: 6/10 (60%) Generation 2: 22/24 (92%) Generation 3: 91/102 (89%)
Marcheix et al., 2007[58]	CoreValve Revalving System	10	1	Aortic stenosis	10/10 (100%)	Retrograde	21 Fr	7/10 (70%)
Berry et al., 2007[59] Berry et al., 2007[60]	CoreValve Revalving System	13 1 (0)	10	Aortic stenosis	11/13 (85%)	Retrograde	21 Fr	11/13 (85%)
Lamarche et al., 2007[61]	CoreValve Revalving System	1	3	Aortic stenosis	1/1 (100%)	Retrograde	21 Fr	1/1 (100%)
Lange et al., 2007[62]	CoreValve Revalving System	1	10 days	Aortic stenosis	1/1 (100%)	Transapical	NA	NR
Wenaweser et al., 2007[63]	CoreValve Revalving System	1	12	Aortic stenosis	1/1 (100%)	Retrograde	21 Fr	1/1 (100%)
Ruiz et al., 2008[64]	CoreValve Revalving System	1	360	Aortic stenosis	1/1 (100%)	Retrograde	25 Fr	1/1(100%)
Totals: CoreValve ReValving System		**251**			**241/274 (88%)** **(23 patients in studies by Grube et al. counted twice)**	**Antegrade (n = 0)** **Retrograde (n = 250)** **Transapical (n = 1)**		**237/273 (87%)** **(10 patients in studies by Grube et al. counted twice)**
Paniagua Heart Valve								
Paniagua et al., 2005[65]	Paniagua Heart Valve	1	5 days	Aortic stenosis	1/1 (100%)	Retrograde	NR	0/1 (0%)

Study (including year of publication)	Valve name (as stated in report)	No. of patients (unique patients)	Follow-up (months)	Clinical indication	Successful implantation rate	Approach	Catheter size	30-day survival
Lotus Valve								
Buellesfeld et al., 2008[66]	Lotus Valve	1	3	Aortic stenosis	1/1 (100%)	Retrograde	21 Fr	1/1 (100%)
Melody Valve								
Rodés-Cabau, et al., 2008[67]	Melody valve	1	3	Pulmonary stenosis	1/1 (100%)	Antegrade	NR	1/1 (100%)
Direct Flow Medical, Inc.								
Schofer et al., 2008[68]	Direct Flow Medical aortic valve	15	1	Aortic stenosis	12/15 (80%)	Retrograde	NR	14/15 (93%)
Totals for all valves:		**542**		**Aortic stenosis (n = 543)** **Pulmo-nary stenosis (n = 1)**	**534/599 (89%)** **(56 patients counted twice, and 1 patient had 2 procedures)**	**Antegrade (n = 37)** **Retrograde (n = 337)** **Transapical (n = 164)** **Aborted antegrade to retrograde (n = 1)** **Aborted retrograde to antegrade (n = 2)** **Aborted procedures (n = 1)**		**505/596 (85%)** **(56 patients counted twice, 2 patients NR)**

[a] Data from 2 patients in this series are also reported in Cribier et al., 2004.[39]

[b] Walther et al., 2008;[48] Walther et al., 2007;[49] and Walther et al., 2008[50] have overlapping patients (see Evidence Table 2 in Appendix C for details). These three studies combined report on 79 unique patients.

[c] Grube et al., 2006;[55] Grube et al., 2007;[56] and Grube et al., 2008[57] have overlapping patients (see Evidence Table 2 in Appendix C for details). These three studies combined report on 223 unique patients.

Abbreviations: Fr = French; n = number of patients; NA = not applicable; NR = not reported.

Table 13. Important variables in published studies of percutaneous heart valve implantation

Variable	Number of reports	Number of patients
Total numbers	32	542
Position:		
Aortic	31	541
Pulmonic	1	1
Valve manufacturers:		
Edwards Lifesciences	17	273
CoreValve	11	251
Paniagua Heart Valve	1	1
Lotus Valve	1	1
Melody Valve	1	1
Direct Flow Medical	1	15
Study type:*		
Case reports	13	13
Case series	19	532
Approach:**		
Transfemoral antegrade	5	37
Transfemoral retrograde	18	337
Transapical	9	164
Antegrade to retrograde	1	1
Retrograde to antegrade	2	2
Aborted procedure	1	1

* Three patients were included in both case reports and case series.

** Total number of studies for this variable is > 32 because some studies reported on multiple approaches.

Number of studies and patients for each type of valve. We identified six manufacturers of percutaneous heart valves through the published, peer-reviewed medical literature. The first valve to appear in the published literature[37] was initially manufactured by Percutaneous Heart Valve, Inc. The device is referred to as "Percutaneous Heart Valve" in the initial published studies. In 2004, Percutaneous Heart Valve, Inc., was acquired by Edwards Lifesciences, LLC. Subsequently, the same device was referred to as the Cribier Edwards valve in published reports. More recent publications refer to that same device as the "Edwards SAPIEN Transcatheter Heart Valve" (or "SAPIEN THV"). Reports in the non-peer-reviewed literature describe the Ascendra Aortic Heart Valve Replacement System as the Cribier Edwards valve for use in transapical,

rather than transfemoral, delivery. The literature identified by our search strategy does not describe whether or how the differently named percutaneous heart valves acquired or manufactured by Edwards Lifesciences have been modified over time. We identified 17 published reports, describing 12 studies, that reported results on a total of 273 unique patients who received a device manufactured by Edward Lifesciences or Percutaneaous Heart Valve, Inc.

The second valve to appear in the published literature is the CoreValve ReValving System. The first generation was delivered via a transfemoral approach using a 25 French (Fr) catheter. The second generation of the valve was delivered via a 21 Fr catheter. The third and current generation is delivered via an 18 Fr catheter. We identified 11 reports, describing 10 studies, that reported on a total of 251 patients who underwent percutaneous heart valve replacement with a CoreValve device.

Finally, we identified a single published report for each of four additional percutaneous heart valves. A case report of the Paniagua Heart Valve, manufactured by Endoluminal Technology Research, was published in 2005.[65] Case reports of the Lotus Valve (Sadra Medical)[66] and the Melody Valve (Medtronics)[67] were published in 2008. A case series that reported on the initial experience of the first 15 patients who received a Direct Flow Medical valve (Direct Flow Medical, Inc.) via a retrograde transfemoral approach was also published in 2008.[68]

Type of studies. Thirteen of the published reports were case reports, and 19 were case series, the latter representing 532 patients. We did not identify any randomized controlled trials, and none of the identified studies included a comparison group.

Variables associated with surgery. Five reports described an antegrade approach via the femoral vein, 18 described a retrograde approach via the femoral artery, and nine described a transapical approach, representing 37, 337, and 164 patients respectively. Only 10 of the reports

described the setting in which the procedure took place (e.g., operating suite, catheter lab), and none described the training or specialty of the person performing the procedure. Successful implantation of a heart valve percutaneously was achieved in 89 percent of cases.

Size of studies and length of follow-up. All of the published reports were non-comparative case reports or series. The largest series involved 136 patients. All included follow-up data 30 days after the procedure or until death of the patient. Eight reports (24 percent) provided follow-up data 1 or more years after the procedure.

Patient population and concurrent and prior treatments. All of the studies included only adult patients. One reported on implantation of a prosthetic valve in the pulmonic position in a young adult with congenital heart disease;[67] all of the remaining studies were conducted in patients with severe aortic stenosis who were considered to be at high surgical risk for conventional aortic replacement surgery. The mean age of patients was greater than 80 years. A small minority of patients had undergone heart valve replacement prior to undergoing percutaneous heart valve replacement.

Hemodynamic success rates. In nearly all patients, successful implantation of a prosthetic heart valve resulted in significant improvement in both valve area and either mean or peak pressure gradient across the replaced valve. Mild to moderate (Grade 1 or 2) paravalvular leaks were reported after the procedure in the majority of patients. Left ventricular ejection fraction was generally not significantly improved.

Harms reported. The estimated 30-day postoperative survival among all patients included in the published reports was approximately 85 percent. We were unable to calculate a precise rate because there was some overlap of patients in a few of the published series, resulting in double counting of 56 patients. This estimate remains unchanged after excluding studies with

overlapping patients from the 30-day survival calculation. Thirty-day mortality was 337/403 (84 percent) for transfemoral approaches and 168/193 (87 percent) for the transapical approach, including duplicate patients and excluding patients with aborted procedures and patients for whom 30-day survival data were not reported. The most common causes of death attributed to the heart valve replacement procedure were myocardial infarction or stroke (n = 22), arrhythmia (n = 8), perforation of the vessels or heart wall (n = 8), and heart failure (n = 7).

Results from Scientific Meeting Abstracts

Table 14 briefly summarizes data from the 12 abstracts identified by our search of scientific meeting presentations. All of the eligible abstracts identified were presented in the year 2008; otherwise eligible abstracts presented in prior years were excluded because the studies they represented were subsequently published in full reports. The 12 abstracts represent 923 patients; despite our attempt to exclude studies that overlapped entirely with fully published report, it is likely that some of the 923 patients represented in the abstracts listed in Table 14 are represented in the fully published reports summarized elsewhere in this report.

Table 14. Summary of scientific meeting abstracts describing studies of percutaneous heart valve implantation

Valve name	Meeting and year	Abstract reference	Sample size	Date last patient enrolled (actual or expected)	Clinical indication	Approach	Country or countries
Edwards SAPIEN							
	TCT 2008	Sack et al., 2008[69]	30	NR	NR	Antegrade (n = 2) Retrograde (n = 28)	Germany
	TCT 2008	Colombo et al., 2008[70]	29	5/08	Aortic stenosis	Transfemoral (n = 23) or transapical (n = 6)	Italy, France
	AHA 2008	Clavel et al., 2008[71]	50	NR	Aortic stenosis	NR (“percutaneous”)	Canada
	AATS 2008	Ye et al., 2008[72]	19	2006	Aortic stenosis	Transapical	Canada
Subtotal Edwards SAPIEN			**128**				
CoreValve ReValving System							
	TCT 2008	Behan et al., 2008[73]	12	NR	Aortic stenosis	NR (“percutaneous”)	France
	TCT 2008	Maier et al., 2008[74]	33	06/08	Aortic stenosis	NR (“percutaneous”)	Netherlands
	TCT 2008	Piazza et al., 2008[75]	646	04/08	Aortic stenosis	NR (“transcatheter”)	Germany, Netherlands, France
	TCT 2008	De Jaegere et al., 2008[76]	47	05/08	Aortic stenosis	NR (“percutaneous”)	Netherlands
	ESC 2008	Jilaihawi et al., 2008[77] Jilaihawi et al., 2008[78]	30	NR	Aortic stenosis	NR (“transfemoral”)	United Kingdom
Subtotal CoreValve			**768**				
Unnamed							
	TCT 2008	Masson et al., 2008[79]	6	NR	Failed mitral (n = 2) or aortic (n = 4) valve	NR (“transcatheter”)	Netherlands

Valve name	Meeting and year	Abstract reference	Sample size	Date last patient enrolled (actual or expected)	Clinical indication	Approach	Country or countries
					bioprosthesis		
	AATS 2008	Doss et al., 2008[80]	21	NR	Aortic stenosis	Transapical (n = 21) vs. sternotomy (n = 30)	Germany
Total			**923**				

Abbreviations: AATS = American Association of Thoracic Surgery; AHA = American Heart Association; ESC = European Society of Cardiology; n = number of patients; NR = not reported; TCT = Transcatheter Cardiovascular Therapeutics

Four abstracts reported on a total of 128 patients who received the Edwards SAPIEN THV, and six abstracts reported the results of five case series involving 768 patients who underwent percutaneous heart valve replacement with the CoreValve Revalving System. An additional two studies involving 27 patients did not report the name of the device, but circumstantial evidence suggests that the Edwards SAPIEN THV was used in both of these studies.

One of the studies presented as an abstract compared a transapical approach (n = 21) to sternotomy (n = 30) in a series of 51 consecutive patients.[80] This study is the only one we identified in our searches of the published and gray literature that involved a direct, albeit non-randomized, comparison. Three abstracts specified that they used a transapical approach, and six used the term "percutaneous" or "transcatheter" without specifying whether a transfemoral or transapical approach was used. None of the studies represented by the meeting abstracts were conducted in the United States; all were conducted in Europe.

Ongoing Clinical Trials

We identified four pertinent ongoing trials on the website, www.clinicaltrials.gov (Table 15). Three of these are non-randomized, open-label, single group assignment treatment studies involving three different valves: the Melody Transcatheter Pulmonary Valve, Edwards SAPIEN THV, and Ventor Embracer Heart Valve. Pulmonary valve insufficiency is the clinical indication for the former, whereas the latter two are enrolling patients with either "heart valve disease" or "aortic valve disease."

Table 15. Summary of ongoing studies of percutaneous heart valves

Valve name	ClinicalTrials.gov identifier	Sponsor	Name of study	Antici-pated enroll-ment	Study start date	Condition treated	Study design	Country or countries
Edwards Sapien	ClinicalTrials.gov ID: NCT00530894	Edwards Lifesciences	PARTNER trial (Placement of AoRTic TraNscathetER valve trial)	1040	4/07	Critical aortic stenosis	Randomized clinical trial. 4 arms: Cohort A: Edwards Sapien THV valve vs. surgical valve Cohort B: Edwards Sapien THV vs. medical therapy	23 centers in United States, Canada, Germany
Melody Transcatheter Pulmonary Valve	ClinicalTrials.gov ID: NCT00688571	Medtronic Bakken Research Center	Melody Transcatheter Pulmonary Valve (TPV) Post-Marketing Surveillance Study	60	10/07	Heart valve disease	Non-randomized, open label, single group assignment treatment study	Germany
Edwards SAPIEN THV	ClinicalTrials.gov ID: NCT00676689	Edwards Lifesciencs	Pulmonic Feasibility Study of the SAPIEN Transcatheter Heart Valve (COMPASSION study)	30	4/08	Pulmonary valve insufficiency	Non-randomized, open label, single group assignment treatment study	United States
Ventor Embracer Heart Valve Prosthesis	ClinicalTrials.gov ID: NCT00677638	Ventor Technologies	Catheter-Based Transapical Implantation of the Ventor Embracer Heart Valve Prosthesis in Patients with Severe Aortic Valve Disease	30	6/08	Aortic valve disease	Non-randomized, open label, single group assignment treatment study	Germany

The fourth ongoing trial represents the first randomized controlled trial of percutaneous heart valves. The Placement of AoRtic TraNscathetER valve trial, or PARTNER Trial, is sponsored by Edwards Lifesciences. According to the listing in ClinicalTrials.gov, "the purpose of this study is to determine the safety and effectiveness of the device and delivery systems (transfemoral and transapical) in high risk, symptomatic patients with severe aortic stenosis."

The start date of the PARTNER Trial was in April, 2007. Estimated study completion date is September, 2014. Anticipated enrollment is 1040. Eligible patients with aortic stenosis who are at high surgical risk (defined as operative mortality of ≥ 15 percent and/or Society of Thoracic Surgeons risk score ≥ 10) will be randomly allocated to receive the Edwards SAPIEN THV percutaneously or undergo conventional surgical valve replacements. Eligible patients who are not candidates for conventional surgical valve replacement (defined as operative mortality or serious, irreversible morbidity ≥ 50 percent) will be randomly allocated to the Edwards SAPIEN THV or medical management (or balloon aortic valvuloplasty, as indicated).

Registries

Our systematic search of the published literature and our extensive search of the gray literature did not identify any ongoing or recently-closed-but-as-yet-unpublished registries of percutaneous heart valves. Information about the four registries summarized in Table 16 was provided to us by Edwards Lifesciencs. These four registries include patients with the Edwards SAPIEN THV in up to 30 sites in Europe. None includes patients in the United States.

Table 16. Summary of registries of percutaneous heart valve implantation*

Registries	Name of study	Purpose	Anticipated enrollment	Study period	Condition treated	Study design	Country or countries
Edwards SAPIEN THV	Registry of Endovascular Critical Aortic Stenosis Treatment (RECAST) trial (formerly I-REVIVE) registry	To demonstrate that the Edwards SAPIEN THV is a safe and effective treatment for elderly patients who are at a high risk, and therefore poor candidates for AVR surgery.	106	1-year follow-up to be completed in January 2009	NR	Edwards SAPIEN THV with retrograde transfemoral delivery system	France
Edwards SAPIEN THV	TRAVERCE (TRAnsapical Surgical DeliVERy of the Cribier-Edwards aortic bioprosthesis)	A first-in-man pilot study to evaluate the feasibility and safety of the transapical surgical delivery and implatantation of the Edwards SAPIEN THV.	172	12/04 to 4/08	NR		Germany, Austria
Edwards SAPIEN THV	SOURCE post market registry		350	NR	NR	Post market registry	30 European sites
Edwards SAPIEN THV*	PARTNER EU trial (Placement of AoRTic TraNscathetER valve trial)	NR	132	NR	Severe aortic stenosis	Non-randomized, open label, multicenter single group assignment treatment study using either a transapical or transfemoral delivery approach	European sites

* Information provided by Edwards Lifesciences, LLC.

Chapter 6. Variables that May Affect Outcomes for Percutaneous Heart Valves (Question 4)

Methods

Question

Question 4 was: What are the variables associated with surgery or setting that may impact outcomes for percutaneous heart valves?

a. What are the different implantation techniques (i.e., position of implantation, delivery, and axis techniques)? What is the evidence of success (i.e., absence of narrowing and regurgitation) and harms?
    i. For percutaneous aortic valves
    ii. For percutaneous mitral valves

Approach

This research question focused on variables associated with surgery or setting that may impact outcomes for percutaneous heart valves. In consultation with experts in cardiology and cardiac surgery, we elected to broaden our focus beyond the specific variables cited in the question to include other variables that usually impact outcomes for surgical procedures and that we expected would be reported in published reports identified by our search strategy. In the end, we considered six general categories of variables: (1) prosthesis characteristics; (2) implantation approach; (3) treatment setting; (4) operator characteristics; (5) type of anesthesia; and (6) patient characteristics. The specific variables considered under each category are listed in Table 17.

Table 17. Variables potentially associated with outcomes for percutaneous heart valves

Prosthesis characteristics:
- Valve design
- Valve size
- Catheter size
- Deployment
- Post-deployment adjustment
Implantation approach:
- Transfemoral antegrade
- Transfemoral retrograde
- Transapical
Treatment setting:
- Surgical operating room
- Cardiac catheterization suite
- Cardiac catheterization suite enhanced with operating room features (“hybrid” setting)
Operator characteristics:
- Medical or surgical specialty
- Experience
Type of anesthesia:
- General anesthesia
- Conscious sedation
Patient characteristics:
- Medical conditions and comorbidities
- Operative risk
- Indication for the procedure

Literature Review Sources and Methods

For Question 4, we considered a subset of the literature identified for Question 3, namely, the 32 fully published reports that met the inclusion criteria for that question. Important data from these articles are summarized in Tables 12 and 13 in the preceding chapter, and in Evidence Table 2 in Appendix C. The methods used to search the published literature, screen potentially relevant citations, and abstract and evaluate data are described in the preceding chapter. In addition to evaluating the published literature, to answer Question 4 we also consulted with

experts in cardiology and cardiac surgery, and incorporated information and perspectives from pertinent, published review articles.[6, 8, 81-87]

For the present question, we excluded data presented at scientific meetings but not yet published in peer-reviewed journals for the following reasons: (1) the data reported in meeting abstracts were insufficient to create sufficiently detailed evidence tables; (2) data presented at scientific meetings often differ from those that later appear in published reports; (3) data presented at meetings are often derived from a subset of patients whose data have undergone only preliminary analysis; and (4) insufficient data are usually presented in the abstracts to identify new patients in ongoing series for which preliminary findings were previously published.

For the purpose of answering Question 4, we used device implantation success rates and 30-day survival rates as outcome measures. These two outcomes were consistently reported in most of the studies, and they serve as reasonable proxy measures for the feasibility of delivering prosthetic heart valves percutaneously, as well as for short-term clinical outcomes.

Results

The evidence derived from the 32 fully published reports identified by our search strategy that pertains to the six categories of variables identified above is summarized in the sections that follow. Because we did not identify any published reports that included primary data from human studies of percutaneous mitral valve replacement, this section of the report focuses exclusively on percutaneous aortic valve replacement.

Prosthesis Characteristics

For four of the six percutaneous valves now in use or in development, we identified a single eligible published study each. Three of these were case reports,[65-67] and one was a case series involving 15 patients;[68] none of the four included a direct comparator. This is insufficient evidence to comment on potential relationships between the design or manufacturer of a valve and clinical outcomes for these devices.

In contrast, we identified 17 reports representing 273 patients and 11 reports representing 251 patients for the Edwards SAPIEN THV and the CoreValve ReValving System, respectively. Implantation success and 30-day survival were 91 percent and 82 percent, respectively, for the Edwards SAPIEN THV (including its precursors, the Percutaneous Heart Valve and the Cribier-Edwards valve), and 88 percent and 87 percent, respectively, for the CoreValve ReValving System. These data do not support definitive conclusions regarding the possible superiority of one of these devices over the other. All of the included studies were either case reports or case series; none included a direct comparator. Given the absence of an experimental design or control group, comparisons across studies are limited by numerous confounding factors, including patient and operator characteristics, clinical indication for the procedure, treatment setting, and secular trends. The inability to distinguish between causative and confounding factors applies to all of the variables considered here that may theoretically impact clinical outcomes associated with percutaneous heart valve replacement.

Larger catheter sizes may limit patient eligibility due to insufficient iliac artery size; they are also associated with greater risk of vascular trauma to iliac or aortic arteries. The potential relationship between decreasing catheter size and improved clinical outcomes is illustrated by the study by Grube et al.,[57] which demonstrated an implantation survival rate of 92 percent and a 30-day survival rate of 89 percent with the smaller, third-generation of the CoreValve system

compared to rates of 70 percent and 60 percent, respectively, with the larger, first-generation delivery system. As discussed in the preceding paragraph, however, it is possible that the improved outcomes observed over time in the series of patients reported in this study are due to factors independent of the smaller catheter size, such as operator experience with the procedure or other variables that may have changed over time.

Although clearly important for transfemoral approaches, the size of the delivery system catheter is theoretically less important for the transapical approach, which does not require canalization of major vessels. There is also a theoretical advantage of devices that permit either post-deployment adjustment or intraoperative deployment of a second percutaneously delivered heart valve within a malpositioned prosthetic valve. The reports we reviewed were not designed to address either of these issues.

Implantation Approach

Three delivery or access approaches have been reported for percutaneous aortic valve replacement: transfemoral antegrade; transfemoral retrograde; and transapical. The transfemoral antegrade route offers the theoretical advantage of femoral venous rather than arterial access, potentially reducing vascular complications. In this approach, a catheter is introduced through the groin into the femoral vein, and then maneuvered to the right atrium and across the intra-atrial septum and mitral valve to reach the aortic valve. This approach carries the risk of residual atrial septal defect from the large delivery catheter required, as well as the risk of procedure-associated mitral regurgitation. In addition, the complexity of this technique prevented widespread adoption of the procedure, particularly with first-generation devices.

In current practice, the transfemoral antegrade approach has largely been replaced by the

transfemoral retrograde approach, which allows a simpler route of delivery. In this approach, a catheter is introduced through the groin into the femoral and iliac arteries to the aorta and then to the aortic valve. Limitations of this approach include the large diameter of the delivery catheter that must be accommodated by the iliac artery, and the tortuosity and atherosclerosis of the aorta in many patients who have aortic stenosis.

Transapical aortic valve replacement is a recently developed option for patients with unfavorable aortic or iliac artery anatomy for the transfemoral approach, and is performed by cardiac surgeons via a left thoracotomy incision. Compared to transfemoral approaches, transapical valve replacement has theoretical advantages associated with the straight-line approach to the aortic valve, including potentially reducing complications of aortic athero-embolic events, bleeding at the site of vascular access, and mitral valve damage. However, this technique carries the potential risks associated with surgical access and general anesthesia. Reported implantation success and 30-day survival rates are 87 percent and 84 percent, respectively, for transfemoral approaches, and 95 percent and 87 percent, respectively, for the transapical approach.

Treatment Setting

Percutaneous heart valve replacements have generally been performed in cardiac catheterization laboratory settings because of the availability of appropriate devices and fluoroscopic imaging equipment for the procedural aspects. To date, the majority of percutaneous valve implantations have occurred under general anesthesia, with the subsequent requirement that the catheterization laboratories used must allow for anesthesia equipment and personnel. Because the procedure involves implantation of a prosthetic device, the maintenance

of a sterile setting is important to reduce the risk of infection.

The advent of percutaneous aortic valve replacement via a transapical approach emphasizes the overlap between cardiac catheterization laboratory and operating suite settings for these procedures. This overlap has led to the development of "hybrid" catheterization laboratories developed and equipped to perform procedures traditionally done in operating suites. In addition to standard catheterization imaging equipment, these hybrid settings may involve ceiling-supported lighting equipment to provide higher lighting output, and heating, ventilation, and air conditioning systems to provide laminar flow diffusion of air typically found in operating suites.

Too few published reports identified by our literature reviewed reported sufficient detail about the treatment setting to determine whether this variable impacts outcomes associated with percutaneous valve replacement.

Operator Characteristics

The intersection of procedural elements described above may stimulate increased collaboration between cardiologists (including both interventional cardiologists and echocardiographers), cardiothoracic surgeons, and cardiac anesthesiologists. Although interventional cardiologists by training have greater experience with percutaneous transfemoral procedures and devices, cardiac surgeons are experienced with techniques necessary for transapical valve replacement, as well as possible repair for vascular access complications and cardiopulmonary bypass and ventricular support. Cross-specialty training may develop, with incorporation of simulation technology for endovascular training.

Too few published reports identified by our literature reviewed reported sufficient detail about operator characteristics to determine whether this variable impacts outcomes associated

with percutaneous valve replacement; however, several authors reported improved outcomes with increased operator experience with a given percutaneous heart valve replacement procedure.

Type of Anesthesia

A theoretical advantage of transfemoral approaches compared to either a transapical approach for percutaneous heart valve replacement or conventional aortic valve surgery is that the former can be administered using conscious sedation, as opposed to general anesthesia. The literature we reviewed did not provide sufficient evidence to comment on the independent risk contribution of general anesthesia versus conscious sedation as they apply to percutaneous heart valve replacement.

Patient Characteristics

A patient's clinical status, coexisting medical conditions, and corresponding operative risk are all variables that significantly impact clinical outcomes for any surgical procedure. With the sole exception of a 21-year-old woman with congenital heart disease who underwent percutaneous heart valve replacement of a previously implanted pulmonic valve prosthesis,[67] all of the patients in the published reports identified by our systematic literature search had symptomatic aortic stenosis with a correspondingly relatively high predicted operative mortality for conventional aortic valve replacement by cardiac surgery with cardiopulmonary bypass. Indeed, these patient characteristics may impact not only procedural success, but more importantly long-term outcomes of percutaneous valve therapies that may not be related to the prosthesis or procedure itself.

The reports identified by our literature search did not provide sufficient evidence to

determine which patient characteristics impact outcomes associated with percutaneous valve replacement. Factors associated with mortality in conventional valve surgery may be applicable to percutaneous valve replacement. These factors include age, functional status, cardiac factors, and medical comorbidity.[7, 14-16]

Chapter 7. Discussion

Conventional mechanical and bioprosthetic heart valves are readily available in the U.S. market. Tissue-engineered valves are in development but none currently have an FDA indication. Important clinical issues in selecting a valve include the technical difficulty of valve replacement, valve durability, hemodynamic performance, complication rates, the need for anticoagulation, and effects on patient important outcomes such as functional status and mortality. From a policy perspective, device costs, procedure costs, availability of specific valve types, and availability of experienced operators are additional considerations.

A large number of published randomized controlled trials and observational studies have evaluated the comparative effectiveness of conventional heart valves in adults. Existing systematic reviews compare mechanical to bioprosthetic valves in the aortic or mitral and tricuspid position, but all of these reviews have important methodological limitations that may bias results. A recent high-quality review compared stented- to stentless bioprosthetic heart valves (BHVs) and found mixed short-term hemodynamic benefits for stentless valves, but with the tradeoff of longer duration cross-clamp and heart-lung bypass times.[28] Only one review compared two stented BHVs,[32] and we did not identify any systematic reviews comparing differing mechanical valves. Systematic reviews that aim to compare valves are challenging. Surgical and anesthetic techniques have improved over time, potentially confounding comparisons across time periods. Valve designs have also changed over time, and those changes are not always reliably reflected by changes to valve names; moreover, valve names are not reported in a uniform manner, complicating accurate valve classification. Many currently marketed valves have not been evaluated in long-term randomized controlled trials, necessitating the incorporation of observational studies, which are more subject to bias.

Percutaneous heart valves have been developed and evaluated by at least six companies. Some of these valves are approved for use in Europe, and most of the published literature originates from this region. The current literature consists of case series and case reports focusing almost exclusively on the Edwards SAPEIN THV valve and CoreValve ReValving Systems. The peer-reviewed literature describes just over 500 patients, assessed as high risk for conventional valve replacement, who have received these valves. This initial experience is promising. Rates of successful implantation are high, and 30-day survival is 85 percent. This compares to an approximately nine percent perioperative mortality rate in lower risk patients, age ≥ 65 years old, undergoing conventional valve replacement.[13]

The first percutaneous heart valve replacement procedures were conducted by accessing the venous system via the femoral vein and passing a catheter through the septum of the heart to reach (and traverse) that aortic valve. This transfemoral antegrade approach now appears to have been replaced by one of two emerging approaches: (1) a retrograde approach via the femoral artery; or (2) a transapical approach via the apex of the heart. Unlike the early transfemoral antegrade approach, the retrograde approach does not require perforating and traversing the septum, but has important technical challenges, in large part because of the calcified and tortuous arteries that must be navigated with a relatively large catheter. In contrast, the more recently developed transapical approach obviates the need for maneuvering a catheter through either arteries or veins, but it requires making an incision in the chest wall.

The transapical approach is performed by cardiac surgeons and would require little new training. The transfemoral approach is often performed by interventional cardiologists but is technically complex and requires additional training. Few groups in the United States have significant experience with this approach. Although the initial experience demonstrates that

percutaneous heart valves can be implanted with good short-term success, longer-term survival, valve durability, and complication rates are unknown. Even comparison of short-term success to historical controls is problematic because predicted mortality is based on imperfect risk prediction models that were developed for other cardiac surgeries. A further limitation of the extant literature is the subjective nature of patient selection as "too high risk for surgery," making appropriate patient selection less certain. The ongoing Placement of AoRtic TraNscathetER (PARTNER) valve randomized controlled trial comparing percutaneous heart valves to conventional valves will be critical in comparing the relative safety and efficacy of these technologies.

Chapter 8. Future Research

The long-term durability of mechanical heart valves is well established and has been shown to be superior to that of early generation bioprosthetic heart valves. Newer generation bioprosthetic heart valves (BHVs) are purported to have improved durability. Since BHVs do not require chronic anticoagulation, durability is a critical issue in determining at what age to recommend BHVs instead of mechanical valves. An updated, high-quality systematic review could address this issue. An updated review may also be able to evaluate specific valves within each class, including currently marketed newer versus older valves and valves with different design features (e.g., mechanical bileaflet versus tilting disc). Because the number of direct comparisons is limited for many valves and some valve classes, indirect comparisons using network meta-analysis may be useful. A recent observational study using Medicare Claims data found BHVs were associated with a slightly lower risk of death and complications, but a higher risk of reoperation in older adults undergoing isolated aortic valve replacement.[34] Claims data provide limited information for case-mix adjustment. Recognizing that randomized controlled trials are not practical for all comparisons, an observational study utilizing claims data coupled with clinical databases could improve case-mix adjustment and estimates of comparative effectiveness.

For percutaneous heart valves, the potential research agenda is broad. What are the complication rates, durability, and effects on mortality and health-related quality of life? How do these valves compare to conventional valve replacement in lower risk patients? Which procedural and setting factors, including procedural volume, are related to clinical outcomes? In which patient populations are percutaneous heart valves indicated? The ongoing Placement of AoRtic TraNscathetER (PARTNER) valve randomized controlled trial will address the efficacy

of percutaneous heart valves compared to medical treatment in high-risk patients, and their efficacy compared to conventional valves in patients at the higher range of acceptable risk for surgical replacement. If percutaneous heart valves become FDA approved, a prospective registry to track the specific devices implanted and the clinical characteristics of recipients could be linked to Medicare claims data for subsequent analysis.

We identified specific opportunities for improved reporting that would facilitate comparative effectiveness studies. Authors of study reports should consistently give the complete valve name as specified by the manufacturer. Since methods for implanting percutaneous heart valves are evolving, detailed reporting of technical factors that may be associated with outcomes – such as details of the implantation approach and characteristics of the operators – would allow for retrospective analysis.

Selection of heart valves involves a number of trade-offs. From the surgeon's perspective, some valves require greater technical expertise and operating times. From the patient's perspective, valve durability and the related risk for reoperation, complication rates, and the need for chronic anticoagulation are all pertinent considerations. From the policymaker's perspective, valve prosthesis costs, costs over the life of the valve (including anticoagulation monitoring for mechanical valves), and access to competing valve replacement options may be relevant considerations. Percutaneous heart valves, if FDA approved, may introduce a new option for patients who are currently deemed too high risk for conventional valve replacement. Because these patients have multiple competing risks for mortality, the effects on all-cause mortality and health-related quality of life are uncertain. From a societal perspective, the introduction of percutaneous valves may require a large investment in clinician training, redesign of procedural suites, and direct costs for heart valve replacement in a population previously not eligible. If

percutaneous valves are proved effective in high-risk patients, a further consideration is whether to extend this procedure to lower risk patients because of its potential for lower morbidity and lower costs. Complex clinical and policy questions such as these can be addressed by decision modeling. For example, decision modeling could simultaneously consider the effects of patient characteristics (e.g., age, comorbid conditions), valve characteristics (e.g., durability), clinical issues (e.g., other indications for anticoagulation), valve-specific complication rates (e.g., major bleeding), costs, and patient preferences on survival and health-related quality of life.

Chapter 9. Conclusions

Because the U.S. population is aging and aortic and mitral valve disease is age-related, heart valve replacement is an important issue both clinically and from the perspective of healthcare policy. Conventional heart valve replacement is a well-established intervention with many available device options, and current evidence suggests similar outcomes with mechanical and bioprosthetic valves. However, current evidence syntheses do not provide sufficient evidence to select specific valves within each of these categories.

Many older adults are not currently candidates for conventional heart valve replacement. Percutaneous valve replacement has been demonstrated to be feasible for aortic stenosis, and short-term outcomes are promising. Several companies are developing these valves, and the reported clinical experience is increasing rapidly. Percutaneous valves have the potential to expand access to valve replacement for a large group of older adults with severe valve disease and concurrent medical conditions that currently preclude surgery. Percutaneous valves also have the potential to substitute for some conventional valve replacements and expand the indications for valve replacements. However, existing data are inadequate to determine the most appropriate clinical role for these valves.

Decision modeling, coupled with high-quality systematic reviews, could inform clinical and policy decisions in the near future. A randomized controlled trial expected to report initial outcomes in 2010 (the Placement of AoRtic TraNscathetER [PARTNER] trial) should yield important efficacy data. Over the longer term, device registries could be established for the purpose to evaluate comparative effectiveness since randomized trials may not be feasible for some clinically important questions.

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Acronyms and Abbreviations

ACC	American College of Cardiology
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
AVR	Aortic valve replacement
BHV	Bioprosthetic heart valve
CCT	Non-randomized controlled clinical trial
CHV	Conventional heart valve
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
EOA	Effective orifice area
EPC	Evidence-based Practice Center
FDA	U.S. Food and Drug Administration
LVMI	Left ventricular mass index
mm	Millimeters
mm HG	Millimeters of mercury
NYHA	New York Heart Association
OR	Odds ratio
PARTNER	Placement of AoRTic TraNscathetER trial
PICO	Patient population, Intervention, Comparison, Outcomes
QUOROM	Quality Of Reporting Of Meta-analyses
RCT	Randomized controlled trial
RR	Relative risk

SRC	Scientific Resource Center
U.S.	United States
WMD	Weighted mean difference